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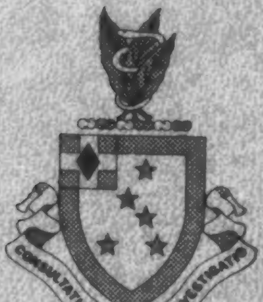
TUMORS of the GALLBLADDER and EXTRAHEPATIC BILE DUCTS

by

JORGE ALBORES-SAAVEDRA, M.D.

and

DONALD EARL HENSON, M.D.



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TUMORS of the GALLBLADDER
and
EXTRAHEPATIC BILE DUCTS

ATLAS OF TUMOR PATHOLOGY

Second Series
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TUMORS OF THE GALLBLADDER AND EXTRAHEPATIC BILE DUCTS

by

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EDITORS' NOTE

The Atlas of Tumor Pathology was originated by the Committee on Pathology of the National Academy of Sciences—National Research Council in 1947. The form of the Atlas became the brainchild of the Subcommittee on Oncology and was shepherded by a succession of editors. It was supported by a long list of agencies; many of the illustrations were made by the Medical Illustration Service of the Armed Forces Institute of Pathology; the type was set by the Government Printing Office; and the final printing was done by the Armed Forces Institute of Pathology. The American Registry of Pathology purchased the Fascicles from the Government Printing Office and sold them at cost, plus a small handling and shipping charge. Over a period of 20 years, 15,000 copies each of 40 Fascicles were produced. They provided a system of nomenclature and set standards for histologic diagnosis which received worldwide acclaim. Private contributions by almost 600 pathologists helped to finance the compilation of an index by The Williams & Wilkins Company to complete the original Atlas.

Following the preparation of the final Fascicle of the first Atlas, the National Academy of Sciences—National Research Council handed over the task of further pursuit of the project to Universities Associated for Research and Education in Pathology, Inc. Grant support for a second series was generously made available by both the National Cancer Institute and the American Cancer Society. The Armed Forces Institute of Pathology has expanded and improved its press facilities to provide for a more rapid and efficient production of the new series. A new Editor and Editorial Advisory Committee were appointed, and the solicitation and preparation of manuscripts continues.

This second series of the Atlas of Tumor Pathology is not intended as a second edition of the first Atlas and, in general, there will be variation in authorship. The basic purpose remains unchanged in providing an Atlas setting standards of diagnosis and terminology. Throughout the rest of this series, the terminology chosen for the World Health Organization's series "International Histological Classification of Tumours" will be used when available. Hematoxylin and eosin stained sections still represent the keystone of histologic diagnosis; therefore, most of the photomicrographs will be of sections stained by this technic, and only sections prepared by other technics will be specifically designated in the legends. It is hoped that in many of the new series a broader perspective of tumors may be offered by the inclusion of special stains, histochemical illustrations, electron micrographs, data on biologic behavior, and other pertinent information when indicated for a better understanding of the disease.

The format of the new series is changed in order to allow better correlation of the illustrations with the text, and a more substantial cover is provided. An index is included in each Fascicle.

It is the hope of the Editors, past and present, the Editorial Advisory Committees, past and present, and the Sponsors that these changes will be welcomed by the readers. Constructive criticisms and suggestions will always be appreciated.

William H. Hartmann, M.D.
Leslie H. Sobin, M.D.

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Jorge Albores-Saavedra, M.D.
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TUMORS OF THE GALLBLADDER AND EXTRAHEPATIC BILE DUCTS

INTRODUCTION

Tumors of the gallbladder and extrahepatic bile ducts are uncommon and difficult to treat. Consequently, they have received less attention than tumors occurring with a higher frequency in other sites. In the United States, cancers of the gallbladder and extrahepatic bile ducts account for less than 2 percent of all malignant tumors, although in many other countries they account for a higher percentage. Because they are rare, much of our knowledge with respect to pathology, histogenesis, and clinical behavior is dependent upon case reports and collected reviews, often published in the surgical literature.

Since first described in 1777, gallbladder cancer has acquired a sinister reputation based on patterns of late diagnosis, unsatisfactory treatment and poor prognosis. Because treatment had not been effective, it was suggested over 50 years ago that surgery be avoided if the diagnosis is established preoperatively (Blalock). Unfortunately, this caveat is still relevant, since more than 75 percent of patients have nonresectable disease at the time of surgical evaluation. The reason for the poor prognosis is the lack of early and specific symptoms which would lead to a diagnosis at a favorable stage. Cases of successful therapy usually result from the accidental discovery of small or in situ cancers in gallbladders removed for cholelithiasis (Bergdahl).

The incidence of gallbladder and extrahepatic bile duct cancer is not uniform throughout the world, but varies in certain racial groups and geographic areas. In the United States, the incidence of gallbladder cancer has stabilized, or possibly even declined, coincidental with a rise in the number of cholecystectomies (Diehl and Beral). However, there are reasons for continued vigilance; one is the observation that pesticides are excreted in the bile and another is the availability of chenodeoxycholic acid for the dissolution of cholesterol stones. The effects of exposing a chronically inflamed gallbladder to chenodeoxycholic acid for long periods are unknown.

A more important reason for vigilance is the increasing use of oral contraceptives. Although the adverse effects of these drugs seem minimal, considering their widespread use, one effect of concern to us is the increased risk of cholelithiasis in women who use these agents. Oral contraceptives have a profound effect on bile composition. They increase cholesterol saturation, which promotes stone formation, by stimulating secretion of cholesterol without changing bile acid or phospholipid secretion (Bennion et al.). Since gallstones, especially those containing cholesterol, are thought to be involved in the etiology of gallbladder cancer, an increase in the incidence of cholelithiasis could possibly lead to an increase in the incidence of gallbladder cancer.

The etiology of carcinoma of the gallbladder remains enigmatic. Infections, gallstones, and benign tumors have been suggested, but there is no experimental proof and only speculation concerning mechanisms.

Because of the similarity of bile acids to methylcholanthrene, investigators have speculated that gallbladder cancer is caused by the conversion of these acids to a substance related to methylcholanthrene. However, attempts to identify methylcholanthrene or other carcinogenic hydrocarbons in the bile have not been successful.

The prospects for improved survival are not encouraging. Since most tumors have already spread beyond the gallbladder by the time of diagnosis, we doubt whether more aggressive surgery would significantly affect prognosis. In fact, there have been no improvements in the treatment of gallbladder cancer in this century. Better chemotherapeutic agents may prolong survival, but it seems more likely that improvements will come through prevention, identification of individuals who are at high risk, and diagnosis of early lesions.

In this Fascicle, we shall review the anatomy and embryology of the extrahepatic biliary tree, stressing those features that bear on the histology of benign and malignant tumors. Most of the Fascicle, however, is devoted to the histologic description of biliary tract tumors with a discussion on classification, early diagnosis, and biologic behavior.

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NORMAL ANATOMY

Practically all textbooks of anatomy recognize the many anatomic variations encountered in the biliary tract. These variations, which include both bile ducts and blood vessels, are of great concern to the surgeon. However, they have no known relationship to the pathogenesis or etiology of biliary tract cancer. The following description considers, therefore, the most common anatomic arrangement.

A pear shaped saccular organ, the gallbladder is normally located under the right lobe of the liver in the gallbladder fossa near the quadrate lobe. It consists of three parts: the fundus, a body, and a neck that tapers into the cystic duct. A small projection or diverticulum, Hartmann's pouch, named for the nineteenth century German anatomist, is often located at the junction of the neck and cystic duct. Originally considered a fourth part of the gallbladder, the pouch is now thought to result from chronic inflammation (see p. 55).

The superior surface of the gallbladder is firmly adherent to the liver, whereas the inferior surface is covered with peritoneum. Occasionally, the gallbladder is freely suspended from the liver by a mesentery or completely buried in its substance. Gallbladders which are attached by a mesentery, the so-called floating gallbladders, are prone to torsion. The inferior surface lies close to the pylorus, duodenum, and hepatic flexure of the colon.

Histology. Histologically, the wall has four layers: (1) a mucosa composed of an epithelial lining and lamina propria; (2) a smooth muscle layer; (3) perimuscular connective tissue; and (4) peritoneum or serosa (fig. 1). The muscle layer, which is most prominent near the neck of the gallbladder, is equivalent to muscularis mucosae of the small intestine. A thicker transverse and circular smooth muscle layer is not present. The perimuscular connective tissue contains nerves, blood vessels, lymphatic channels, and scattered paraganglia. The paraganglia are usually found adjacent to nerve fibers and ganglion cells (fig. 2). Along the hepatic surface, no serosa exists, and the perimuscular connective tissue is continuous with the interlobular connective tissue of the liver.

The mucosa is thrown into multiple irregular folds that flatten as the gallbladder fills and its lumen expands. During contraction, these folds come together and increase in height (Castellucci and Caggiati).

The epithelium consists of a single layer of tall uniform columnar cells supported by a PAS positive basement membrane. The cells have ovoid basal nuclei and a pale cytoplasm that occasionally contains small vacuoles (fig. 3). Functionally, the cells secrete sulfoglycoproteins, some of which are related to the glycoproteins secreted by the intestine (Hakkinen and Laitio). Interspersed among the columnar cells are scattered narrow and dark staining cells which have been referred to as pencil-like cells (Togari and Okada; fig. 3). These cells are considered to be modified columnar cells, although their nature and functions are unknown. Because of their increased enzymatic activity, it is unlikely that these cells are effete (Yamada) or represent an artifact of fixation.

Basal cells, which are smaller than columnar cells, are located immediately above the basement membrane. They are

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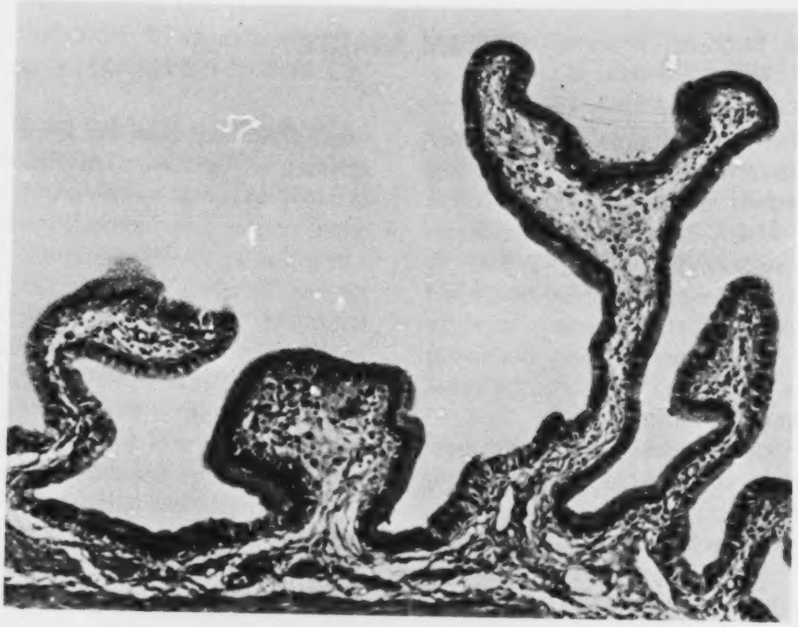

Figure 1
NORMAL HUMAN GALLBLADDER
The mucosal folds are of different height and width. The lamina propria and part of the muscle coat are also shown. X100.*

usually round with ovoid or elongated nuclei whose long axis is parallel with the basement membrane (fig. 3). These cells, which are not numerous, are usually scattered along the epithelium. They are always separated from the lumen by the taller columnar cells and should not be confused with intraepithelial lymphocytes, which are more common. Goblet cells have been described in the fetal human gallbladder, but are not found in the normal gallbladders of adults (Koga). Mucin-secreting glands, which differ morphologically and histochemically from antral type glands, are normally present only in the neck of the gallbladder (Laitio and Nevalainen, 1975a). In abnormal gallbladders showing intestinal metaplasia, argyrophil and argentaffin cells are found in the epithelium (Laitio and Nevalainen, 1975b; Christie). These endocrine cells are seen along the surface and in metaplastic glands.

Aberrant bile ducts (Luschka's ducts), which are remnants of the embryonic primordium of the liver, are occasionally seen in the perimuscular connective tissue adjacent to the liver. Lined by a cuboidal biliary type of epithelium, they are found in 10 percent of gallbladders removed for cholelithiasis.

Ultrastructure. Three types of epithelial cells — ordinary light columnar cells, dark pencil-like cells, and basal cells — occur in the normal gallbladder (Evett et al.). The light columnar cells are most common, comprising about 99 percent of the epithelium. Both the columnar and pencil-like cells are covered with microvilli and rest on

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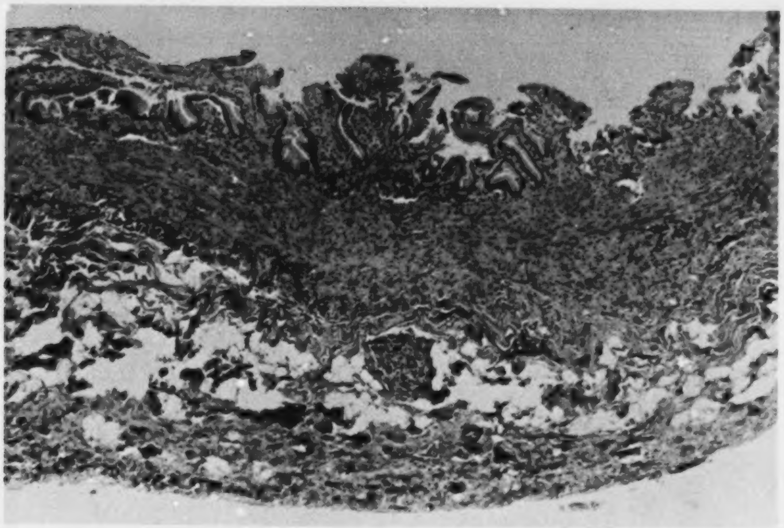
*Throughout the Fascicle where the stain is not designated, the hematoxylin and eosin stain has been used.



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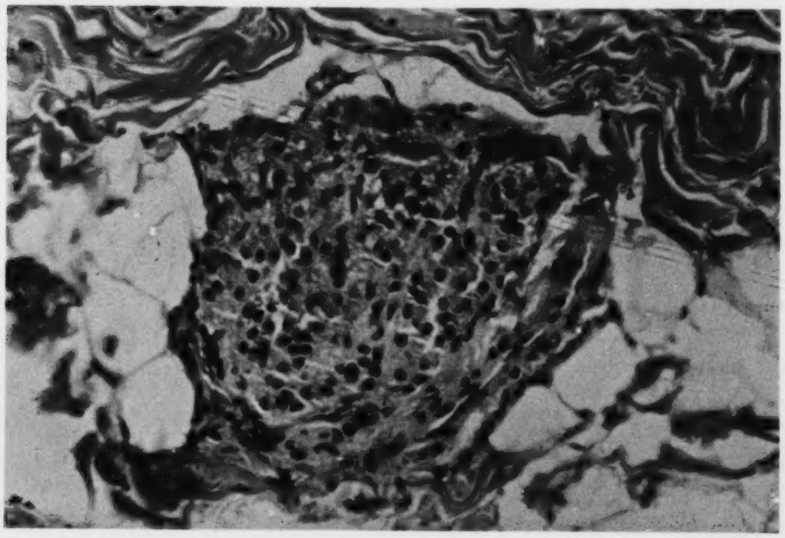

B

Figure 2
PARAGANGLION
(A) Well defined paraganglion in the perimuscular connective tissue of the gallbladder. X40. (B) Higher magnification of paraganglion. X250. (From Fine, G. and Raju, U.B. Paraganglia in the human gallbladder. Arch. Pathol. Lab. Med. 104:265-268, 1980.)

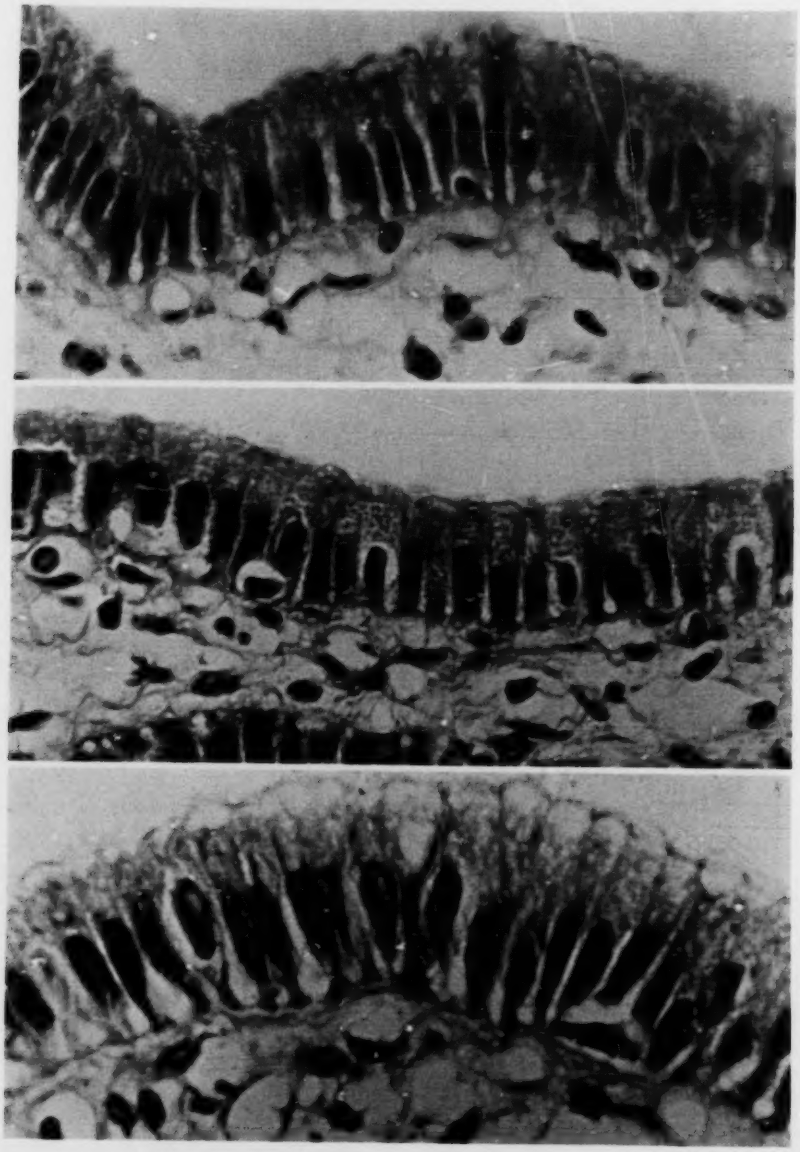

Figure 3
NORMAL EPITHELIUM

Normal epithelium of the fundus and lateral walls of the gallbladder. The columnar cells rest on a basement membrane, some contain small mucous vacuoles in the apical cytoplasm (bottom). A pencil-like cell, which is thinner and darker than surrounding columnar cells is seen in the center of the field (top). A basal cell with clear cytoplasm is located inside the basement membrane (bottom). Its nucleus lies parallel to the basement membrane. Small (top) and large (middle) intraepithelial lymphocytes are also present. These lymphocytes are more common than basal cells. X680.

a basal lamina similar to that which underlies all epithelia (figs. 4, 5). The basal cells are confined to the region of the basal lamina and do not reach the lumen.

Adjacent cells are connected by junctional complexes located at the apical ends of the lateral walls. These walls have complex membrane interdigitations and are separated by intercellular spaces. Fluid transport occurs through the junctional complexes and lateral spaces. These spaces are thought to widen according to the rate and direction of fluid transport (Frizzell and Heintze).

Most cytoplasmic organelles are located in the supranuclear region and consist of mitochondria, rough endoplasmic reticulum, a prominent Golgi apparatus, lysosomes, and a variety of vesicles and granules. The vesicles and granules contain mucin or lipid material. Pinocytic vesicles which are found along the apical surface seem to provide morphologic evidence for another mechanism of absorption. Mitochondria are most numerous in the supranuclear area and may be partially surrounded by rough endoplasmic reticulum. In the human, mucus production is not prominent, but becomes excessive in some pathologic conditions such as chronic cholecystitis (Fox), benign epithelial tumors, and adenocarcinomas. The mucous secretory granules are released by a process called reverse pinocytosis (Koga).

The pencil-like cells are characterized by a dark and narrow profile and a well developed rough endoplasmic reticulum located above the nucleus. Comprising about 1 percent of all columnar cells, they can be recognized by light microscopy (Hayward). Found in many species, these pencil-like cells have also been referred to as peg cells and dark cells. These cells are dispersed along the epithelium, occurring singly, although often increasing in chronic cholecystitis.

The basal cells are randomly distributed along the epithelium. They tend to be ovoid or elongated and have some mitochondria, which usually surround the nucleus, and little endoplasmic reticulum. The cytoplasm forms complex interdigitations with adjacent columnar cells. They are similar to basal cells in other sites.

Under the scanning electron microscope, the mucosal surface consists of rolling, branching folds covered by uniform epithelium (Laitio and Nevalainen, 1972; Schaff et al.; fig. 6). The epithelial cells tend to have regular polygonal or hexagonal boundaries and a slightly convex surface covered with microvilli (fig. 7). This structural arrangement corresponds, in many respects, to the surface architecture of the stomach and small intestine. Mucosal changes revealed by scanning electron microscopy in some pathologic conditions have also been published (Schaff et al.; Myllarniemi and Nickels).

Blood Supply. The gallbladder receives its main blood supply from the cystic artery, a branch of the hepatic artery, while the common bile duct is supplied by the retroduodenal artery, a branch of the gastroduodenal artery. Venous blood drains via the cholecystic veins which arise from a network of small vessels located in the perimuscular connective tissue. This network is continuous with a similar plexus that surrounds the extrahepatic bile ducts. The cholecystic veins usually pass directly into the liver, where they subdivide into superficial and deep capillaries or, less frequently, empty into the portal system. The lymphatic channels, which are important in the consideration of metastases, enter a

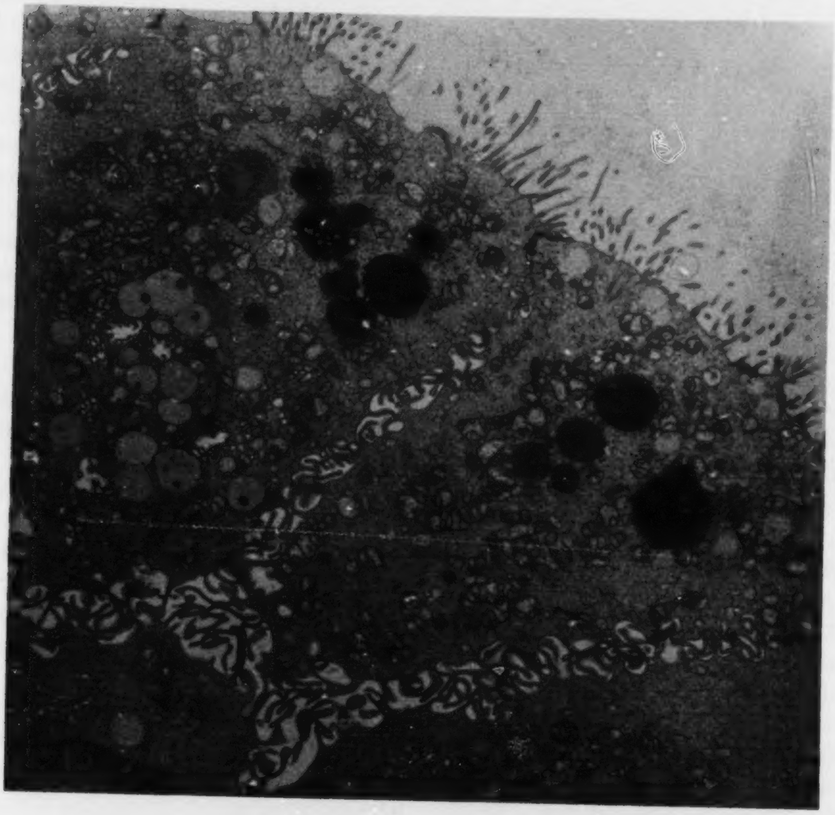

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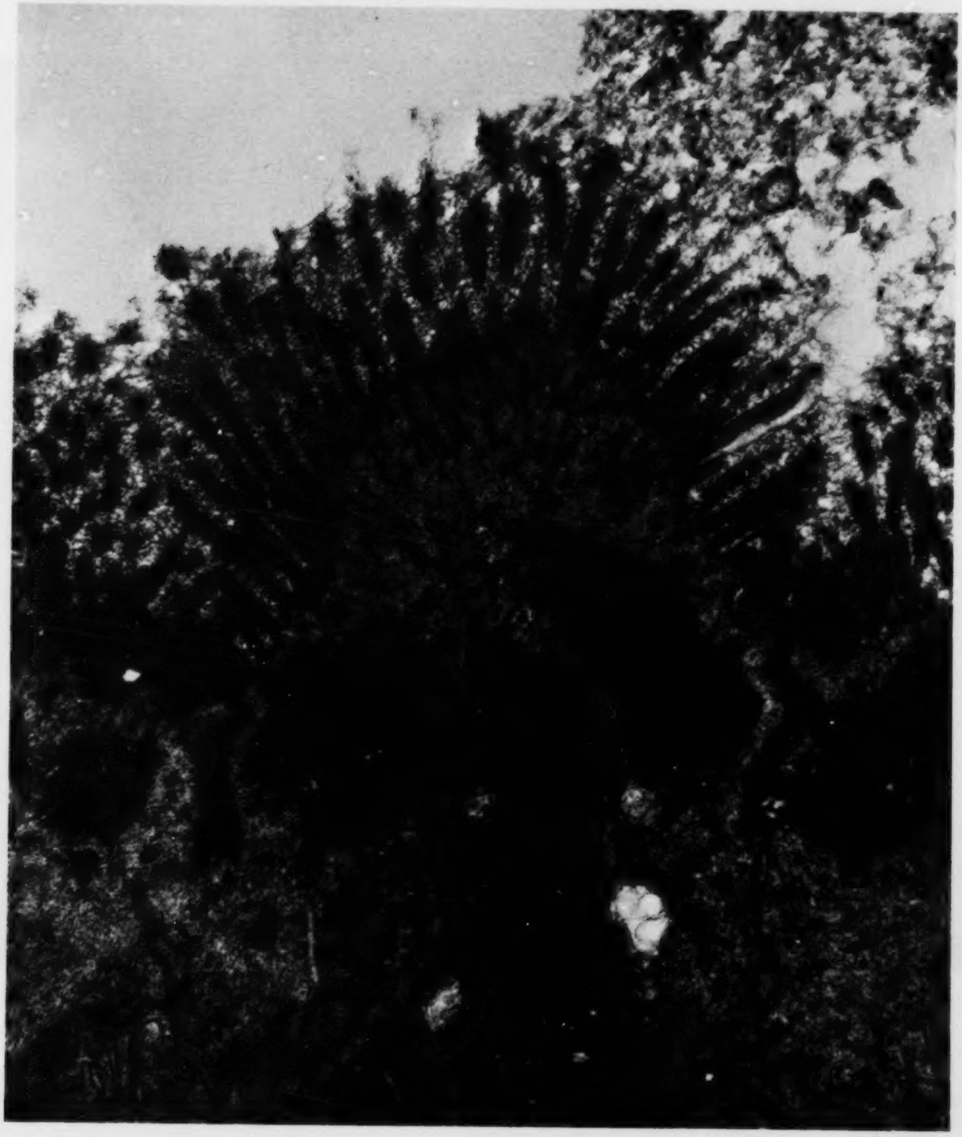
Figure 4
ULTRASTRUCTURE OF NORMAL COLUMNAR CELLS

(A) Tangential section through several columnar cells which are covered by microvilli and contain mucin droplets, mitochondria, and large electron dense bodies. Note prominent intercellular spaces. X3350. (B) Portions of three columnar cells showing microvilli with filamentous glycocalyx. The apical cytoplasm contains large electron dense granules which probably represent mucin. A junctional complex is also visible. X19,500.



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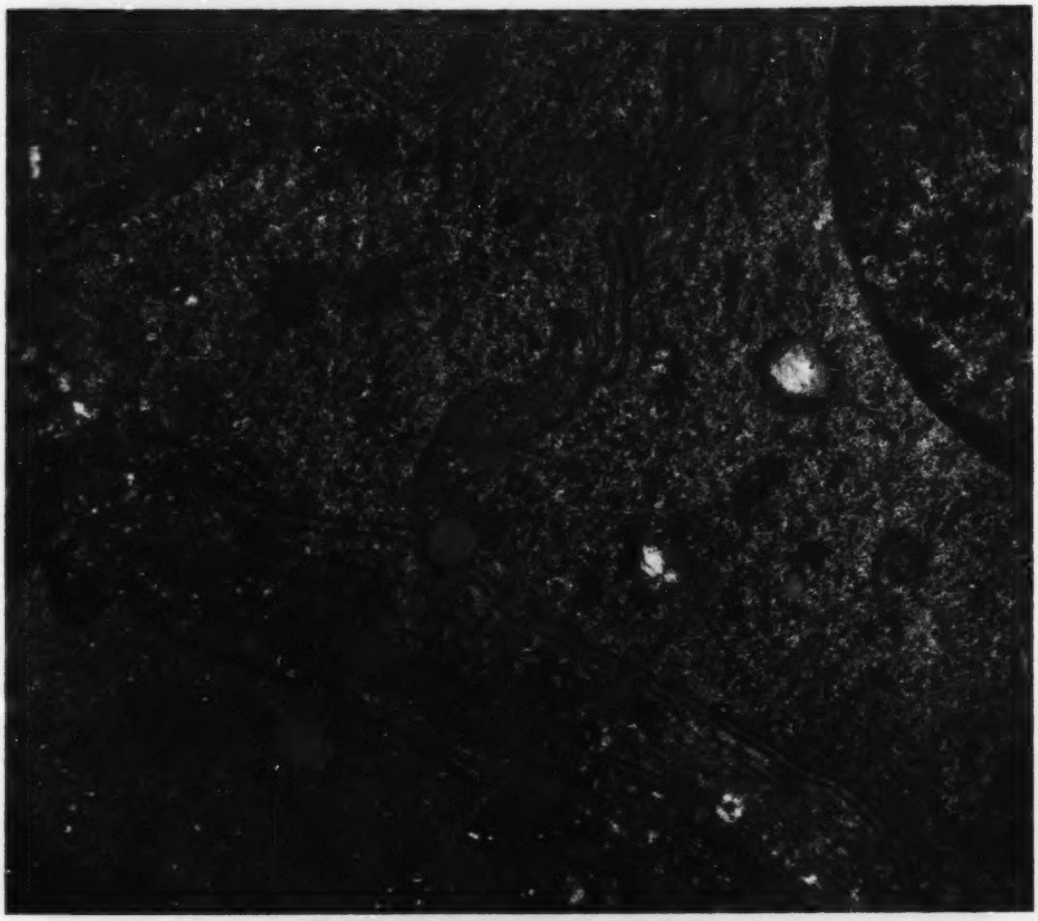

Figure 5
ULTRASTRUCTURE OF NORMAL COLUMNAR CELLS

The basal cytoplasm of two cells rests on the basal lamina. Note the complex interdigitations of the lateral cell membranes. Many glycogen particles, some mitochondria, lysosomes, and some rough endoplasmic reticulum are also present. The lamina propria contains many collagen fibers and a capillary. X19,500.

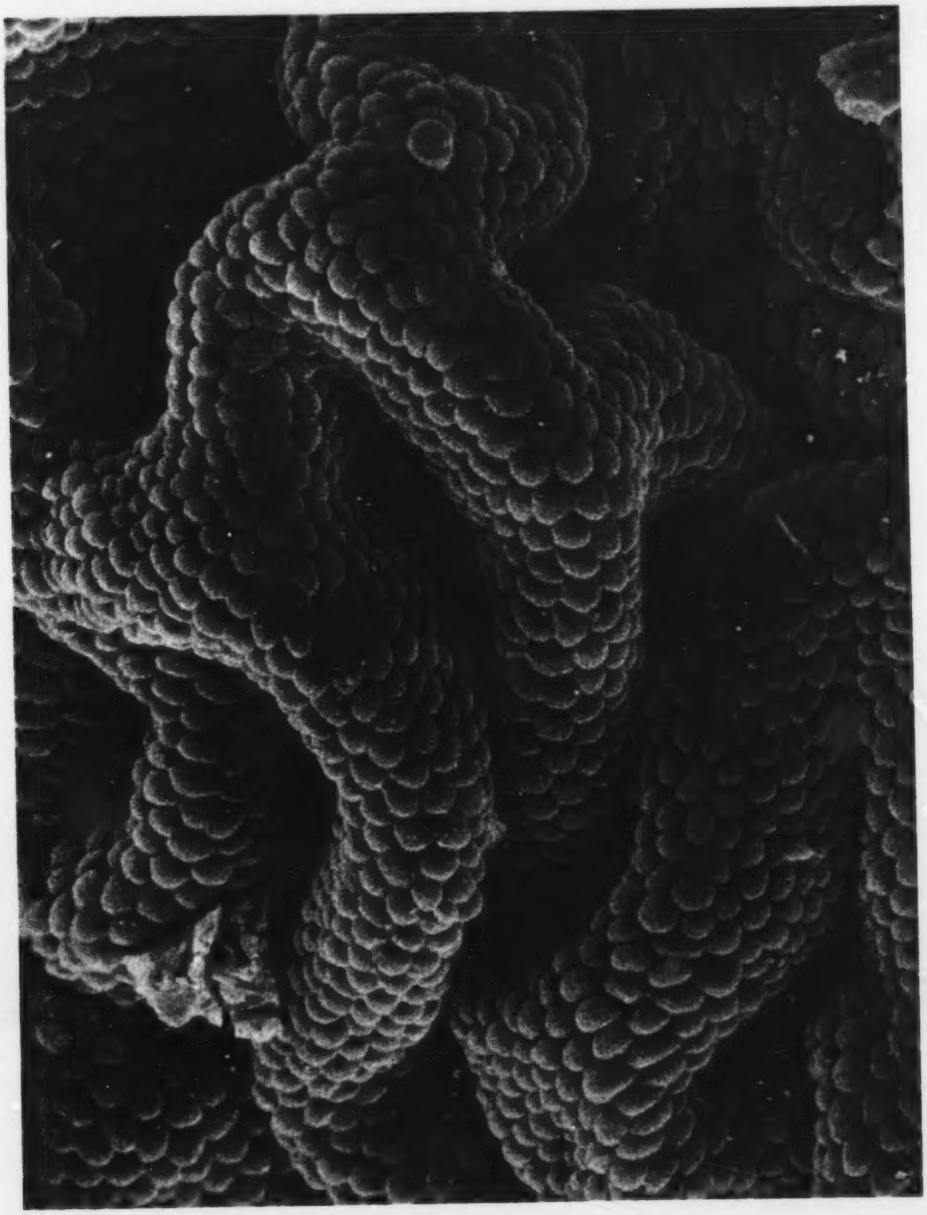

Figure 6
NORMAL MUCOSA

Scanning electron micrograph of gallbladder mucosa. The surface is composed of small rolling folds covered by uniform epithelial cells. X1500. (From Schaff, Z., Lapis, K., and Csikos, A. Scanning electron microscopic study of human gallbladder mucosa in cholelithiasis. Acta Morphol. Acad. Sci. Hung. 27:107-114, 1979.)

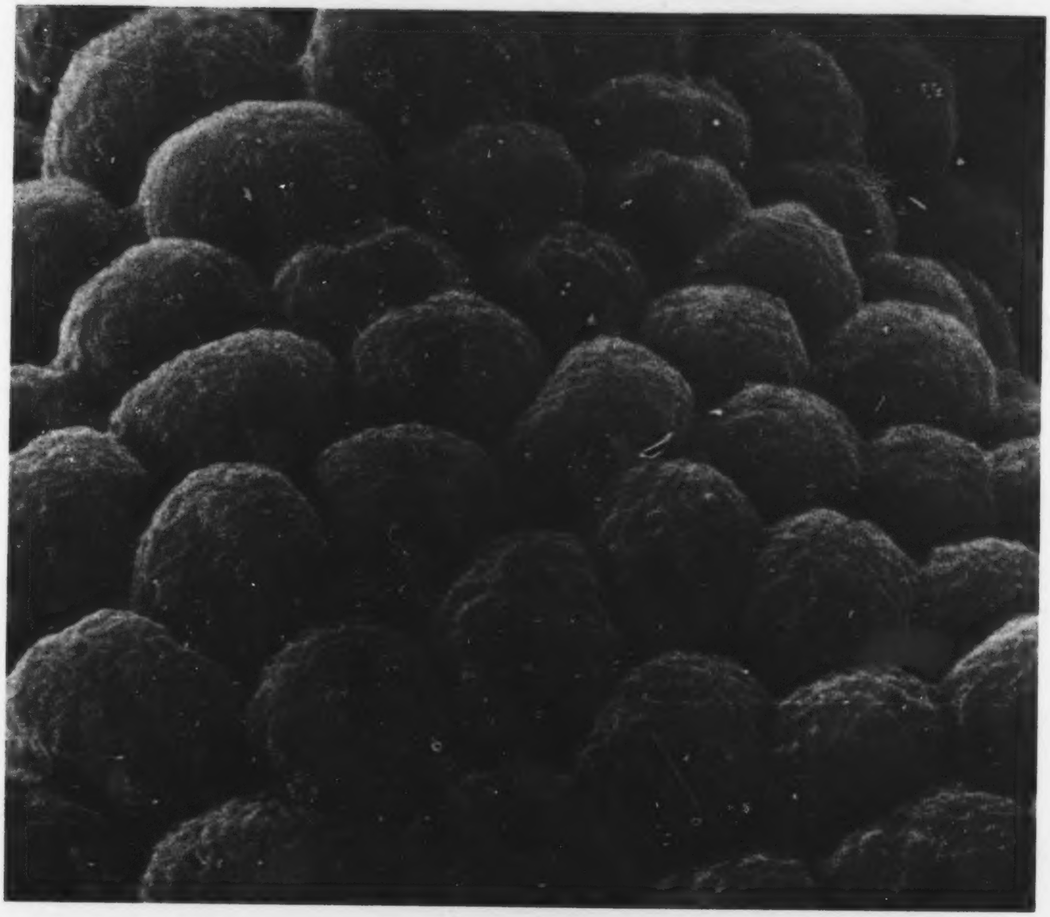

Figure 7
NORMAL MUCOSAL CELLS

Scanning electron micrograph showing normal epithelial cells. The cells, which are separated by deep intercellular clefts, have rounded tops and are nearly identical in size and shape. X1800. (Courtesy of Dr. Z. Schaff and Dr. K. Lapis, Budapest, Hungary.)

sentinel lymph node, the pericholedochal, usually located near the origin of the cystic duct. From here, the lymph flow is toward the peripancreatic nodes.

Extrahepatic Bile Ducts. The cystic duct, whose length can vary from 0.4 to 6.5 cm (Moosman and Coller), connects the gallbladder to the common hepatic duct to form the common bile duct. Its structure is similar to that of the gallbladder (Repassy et al.). However, prominent mucosal folds, the valves of Heister, give the duct a spiral appearance.

Emerging from the liver, the left and right extrahepatic bile ducts join to form the common hepatic duct which descends lateral to the hepatoduodenal ligament. The common hepatic duct then connects with the cystic duct to form the common bile duct which passes behind the first part of the duodenum and traverses the head of the pancreas until it opens into the second part of the duodenum at the ampulla of Vater. The common hepatic duct can vary from 0.8 to 5.2 cm in length, while the common duct, exclusive of the ampulla, varies from 1.5 to 9.0 cm. In general, the diameter of the common duct increases with age (Millbourn).

The common duct is divided into three parts in relation to the duodenum and pancreas: supraduodenal, which is the longest part; retroduodenal; and pancreatic. The supraduodenal part is usually that segment explored by the surgeon.

Lined by a single layer of tall columnar cells, the mucosa of the bile ducts usually forms irregular pleats or small folds that run longitudinally. The subepithelial connective tissue contains numerous elastic fibers, while muscle fibers, which are aligned parallel to the lumen, are generally absent or sparse, except near the sphincter of Oddi. Small intramural mucous glands that increase in number toward the distal part open into the lumen in small pits, the sacculi of Beale. As undeveloped remains from the hepatic diverticulum, these glands are considered embryonic vestiges.

Congenital Variations. The important vascular and ductal variations encountered during surgery have been reviewed (Benson and Page). Variations in the vascular supply are found in more than 50 percent of patients undergoing cholecystectomy. Variations of the ducts, on the other hand, are much less frequent, occurring in 14 percent of all cholecystectomies. By combining these figures, it becomes obvious that a surgeon can expect some type of anatomic variation in every other operative case.

The most common vascular variations include an accessory cystic artery, anterior transposition of the cystic or the right hepatic artery, or both, and a relatively short cystic artery that arises from the right hepatic artery. Variations in the vascular supply to the bile ducts and their implications for postoperative strictures have also been described (Northover and Terblanche).

The two most common ductal variations include a long cystic duct fusing low with the common duct and high fusion of the cystic and hepatic ducts.

Congenital anomalies such as double gallbladder, cysts, anomalies of position, atresia of the bile ducts, and agenesis of the gallbladder are infrequently encountered and will not be discussed.

Embryological Development. The gallbladder originates in the fourth week of fetal life as a ventral medial outgrowth that buds from the primitive endoderm near the junction of the foregut and yolk sac, opposite the dorsal pancreatic bud. This outgrowth pushes into splanchnic mesenchyme and becomes the hepatic diverticulum. The cranial part differentiates into the liver and intrahepatic bile ducts, while the caudal part branches to form the gallbladder and cystic duct. A small bud, the ventral pancreas, which eventually becomes part of the head of the pancreas, arises from the hepatic diverticulum near its origin from the foregut. The original hepatic diverticulum then elongates to form the common bile duct. By the time the embryo reaches 5 mm, or five weeks, the gallbladder is a small tubular structure lined by epithelium and connected to the common duct by a short stem, the future cystic duct.

As the stomach rotates, causing torsion on the duodenum, the hepatic diverticulum comes to lie dorsal to the duodenum and the small ventral pancreas comes around to fuse with the much larger dorsal pancreas, which is now ventral, to form the head and uncinate process. As a result of fusion, the ventral pancreatic duct becomes the proximal segment of the main pancreatic duct (duct of Wirsung) which, because of its origin from the hepatic diverticulum, usually opens into the duodenum through the terminal part of the common bile duct.

By the eighth week of gestation, a lumen has been established throughout most of the biliary tract. The layers of the gallbladder are fully differentiated when the fetus reaches 15 to 18 weeks. Bile secretion by the fetal liver first takes place around the third month of gestation.

In addition to explaining the occurrence of congenital defects, knowledge of the embryology is important for understanding the pathogenesis of certain lesions found in the biliary tract. For instance, ectopic tissue is occasionally seen in the gallbladder or bile ducts. This misplaced tissue, which includes gastric, pancreatic, or liver heterotopia (Bassis and Izenstark), may be discovered accidentally in cholecystectomy specimens or cause symptoms, especially in patients under 25 years of age.

To account for this ectopia, pathologists have traditionally considered two possibilities: (1) heteroplastic differentiation or (2) displacement, during fetal development, of tissue committed to differentiate into other structures. Except for ectopic adrenal tissue (Busuttil), all combinations of ectopia reported in the biliary tract have been anatomical derivatives of the primitive foregut.

On the other hand, certain histologic changes, including the differentiation of tumors, depend on the propensity of the biliary epithelium to revert to its tissue of origin in response to pathologic stimuli. This reversion, which also occurs in other organs, is manifested by a shift in the histologic and antigenic differentiation toward intestinal mucosa. For example, the gallbladder epithelium can undergo intestinal metaplasia acquiring intestinal associated antigens which are not present in normal gallbladder mucosa (De Boer and Nairn). Specific types of intestinal metaplastic changes that are observed, often in cases of chronic cholecystitis, include goblet cells, Paneth cells, superficial gastric-type epithelium, and antral-type gland formation. Adenocarcinomas that resemble intestinal mucosa can arise in the gallbladder, and papillary tumors with intestinal epithelial structures have been known for years. As with the gallbladder, the liver can also revert to its tissue of origin. In laboratory animals, liver tumors induced chemically can differentiate toward intestinal epithelium (Yoshida et al.).

FUNCTION

The functions of the gallbladder are (1) concentrating and storing bile (Rous and McMaster) and (2) propelling the bile into the duodenum in response to a meal, where it facilitates digestion and absorption of fats (Boyden).

By absorption of water against osmotic gradients, the gallbladder can concentrate bile to less than 20 percent of its original volume. Absorption is coupled to an electrically neutral sodium chloride influx process which is inhibited by agents that elevate intracellular levels of cyclic 3',5'-adenosine monophosphate (Frizzell et al.). Physiologic studies indicate that the gallbladder mucosa, at least in normal animals, consists of a single functional cell type, capable of absorbing NaCl and water, but not sugars or amino acids. It should be emphasized, however, that most work on gallbladder physiology has been conducted in laboratory animals, and presumably the results apply to man.

Contraction of the gallbladder is largely mediated by cholecystokinin, a peptide hormone secreted by the duodenum and upper small intestine and also found in the brain (Synder). Patients with cholesterol gallstones tend to have an increased sensitivity to cholecystokinin (Northfield et al.). Relaxation of the gallbladder is caused by vasoactive intestinal peptide (Said). Secretin, another peptide hormone secreted by the duodenum, inhibits the concentrating mechanism and prevents water absorption. Somatostatin, a small peptide hormone secreted by D cells, inhibits gallbladder contraction and bile flow. Excess production of somatostatin, as in D cell tumors (somatostinomas), leads to bile stasis and stone formation. The actions of these peptide hormones are complex, since secretin and cholecystokinin also stimulate somatostatin release. In guinea pigs, the muscle layer contains receptors for histamine (Waldman et al.).

In addition to storage and contraction, the gallbladder can also be considered a secretory organ. The epithelium secretes glycoproteins, the rate of which depends on the composition of the diet. Secretion tends to increase following a fatty meal or a lithogenic diet and decreases during fasting. Secretion is also increased after stimulation of the small cholinergic nerves that innervate the gallbladder (see review by Soloway and associates for references).

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◆

BENIGN TUMORS OF THE GALLBLADDER

BENIGN EPITHELIAL TUMORS

Adenoma

SYNONYMS AND RELATED TERMS: Adenomatous polyp; papilloma; polyp.

As in the intestine, adenomas can be divided into three types — tubular, papillary, and mixed. The tubular type, which is most common, is composed of compact glands, whereas the papillary type has branching treelike projections lined by epithelium. Some adenomas display a mixed tubular and papillary pattern.

Adenomas are usually discovered incidentally during cholecystectomy or as fixed radiolucent defects on cholecystograms (fig. 8). They are often asymptomatic unless they obstruct the cystic duct or neck of the gallbladder (McGregory and Cordiner). Signs and symptoms are similar to those caused by cholelithiasis and include pain, postprandial distress, and, occasionally, a palpable gallbladder. In many cases, however, the signs and symptoms seem to result from stones or inflammation and not directly from the tumor. In contrast to malignant tumors in which there is a high incidence of stones, benign tumors are associated with stones in less than 50 percent of cases (Ochsner

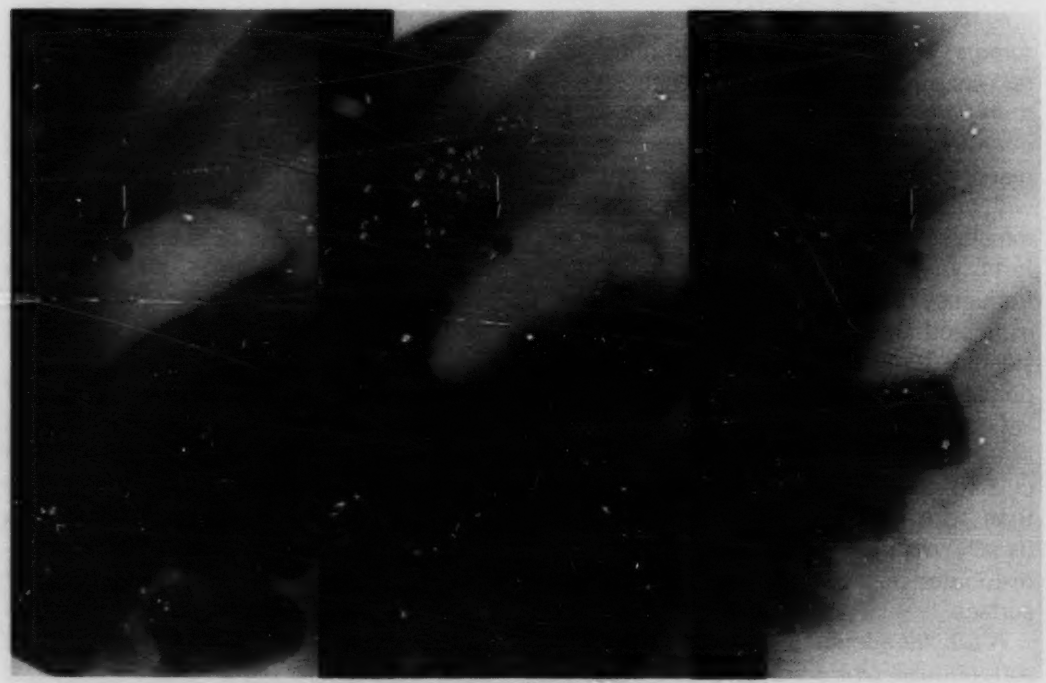

Figure 8
ADENOMA
A discrete radiolucent area is present in this roentgenogram. This appearance is characteristic of adenomas of the gallbladder. (Fig. 17 from Fascicle 26, First Series.)

and Ochsner). In about one-third of cases the adenomas are multiple.

There does not seem to be any statistical association between adenomas arising in the gallbladder and those in the intestine. Occasionally, however, adenomas of the gallbladder are found along with adenomas in the intestine. Tubular adenomas have occurred in the gallbladder in a patient with Gardner's syndrome (Tantachamrun et al.) and in another with the Peutz-Jeghers syndrome (Foster and Foster).

Opinions, which often reflect the fashions of the day, have varied regarding the cause of these lesions (Arbab and Brasfield). None of these explanations have been accepted.

Incidence. There is no information available regarding the true incidence of benign tumors, although in considering published reviews, their operative incidence is less than 1 percent of all cholecystectomies. In our material of 4000 cholecystectomy specimens, their incidence is 0.5 percent. As with carcinomas, they are more common in females and usually occur after the age of forty. In the literature before 1950, the frequency of benign tumors was often overestimated by including lesions now considered tumor-like, such as cholesterol polyps (Tabah and McNeer).

Gross Features. Most tubular and papillary adenomas are single, sessile or pedunculated, and small, measuring as a rule less than 2 cm in diameter. When multiple, they usually vary from two to nine and may be distributed over a large area of the mucosal surface.

A tubular adenoma initially appears as a soft, nodular, pink elevation on the mucosa. As the lesion enlarges, it projects into the lumen, becoming pedunculated. At this stage the adenoma resembles a lobulated berry-like nodule similar to the tubular adenomas of the large intestine (figs. 9, 10). Papillary adenomas exhibit the typical cauliflower-like appearance with a fine granular surface (fig. 11).

Microscopic Description. Tubular adenomas are characterized by closely packed glands lined by cuboidal or columnar cells usually containing more cytoplasmic mucin than normal gallbladder epithelium. The glands are usually small, but in some adenomas they can be dilated or cystic (figs. 12, 13). Variations occasionally seen in the epithelium include squamous metaplasia, colonic-type epithelium, or areas that resemble intestinal mucosa with argyrophil and Paneth cells (figs. 14, 15). The connective tissue stroma is usually minimal, but can become edematous or partially hyalinized and may contain lymphocytes. It is continuous with the connective tissue in the lamina propria. The glands proliferate in a diffuse and random manner, although in some tumors they form distinct lobules (figs. 16, 17).

When the connective tissue stroma is abundant and edematous and there are only scattered glands, the microscopic picture is reminiscent of a fibroadenoma of the breast (Ochsner and Carrera).

Papillary adenomas are composed of delicate or coarse connective tissue stalks extending into the lumen and covered by a single layer of cuboidal or columnar epithelium (fig. 18). Some papillary adenomas are indistinguishable from those of the intestine (figs. 19, 20). A large sessile tumor of this type containing argyrophil and Paneth cells caused an electrolyte imbalance by excreting excessive chloride (Kerr and Lendrum).

Foci of in situ carcinoma have occasionally been observed in tubular or papillary

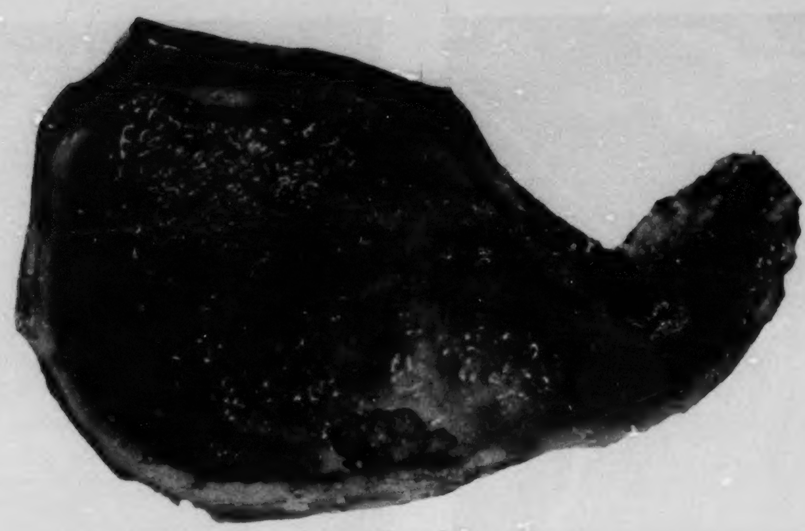

Figure 9
TUBULAR ADENOMA
This small tubular adenoma, which has a fine nodular surface, arose from the lateral wall. Multiple stones had been previously removed from the gallbladder. The adenoma was an incidental finding.

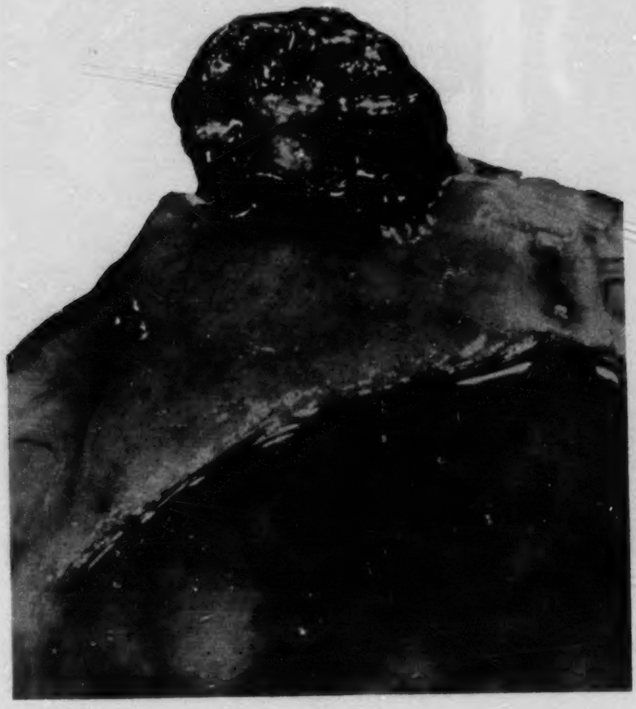

Figure 10
TUBULAR ADENOMA
A small sessile nodule on the mucosal surface. The gallbladder has been everted to expose the nodule, which, histologically, was a tubular adenoma.

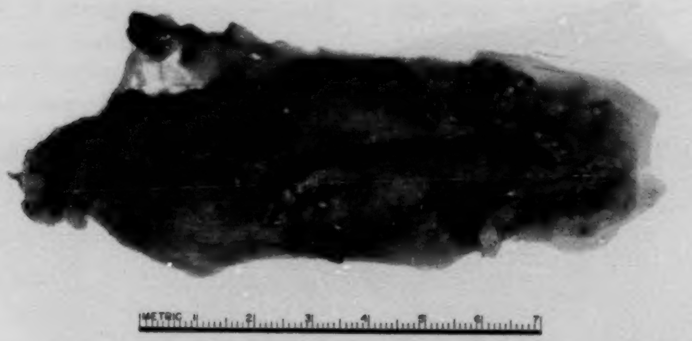

Figure 11
PAPILLARY ADENOMAS
Eight small papillary adenomas project from the mucosa of the gallbladder. Some of these are pedunculated, while others appear sessile. (Fig. 18 from Fascicle 26, First Series.)

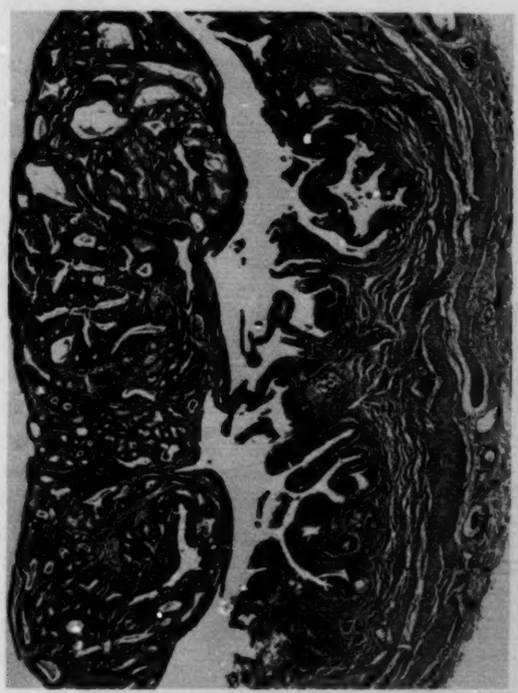

Figure 12
TUBULAR ADENOMA
A pedunculated tubular adenoma is composed of closely packed glands which vary in size. X30. (Fig. 21 from Fascicle 26, First Series.)

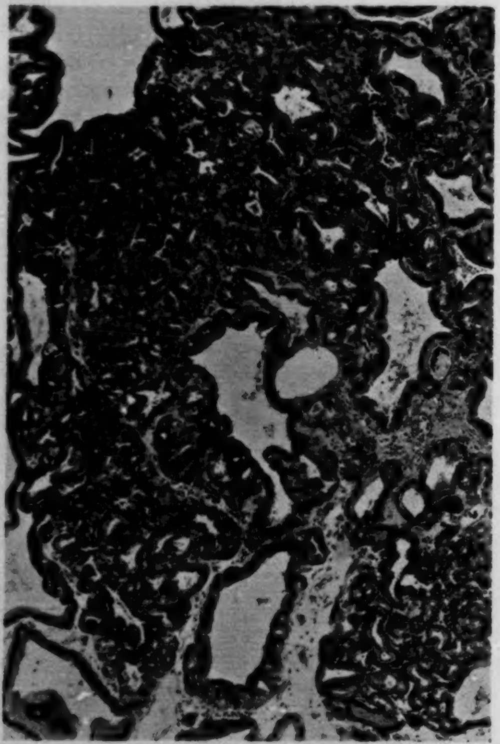

Figure 13
TUBULAR ADENOMA
Most glands are small and closely packed, although some are cystically dilated. All glands are lined by tall columnar, mucus-secreting epithelium. X35. (Courtesy of Dr. H. Battifora, Duarte, CA.)

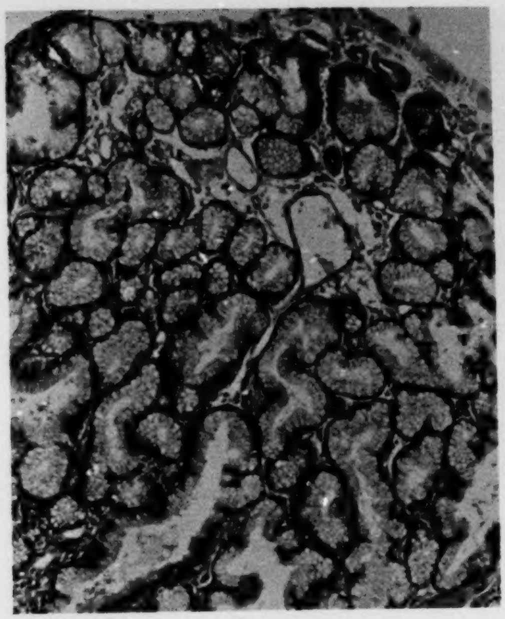

Figure 14
TUBULAR ADENOMA
Most glands are lined by tall columnar mucus-secreting epithelium similar to that of tubular adenomas of the large intestine. X100.

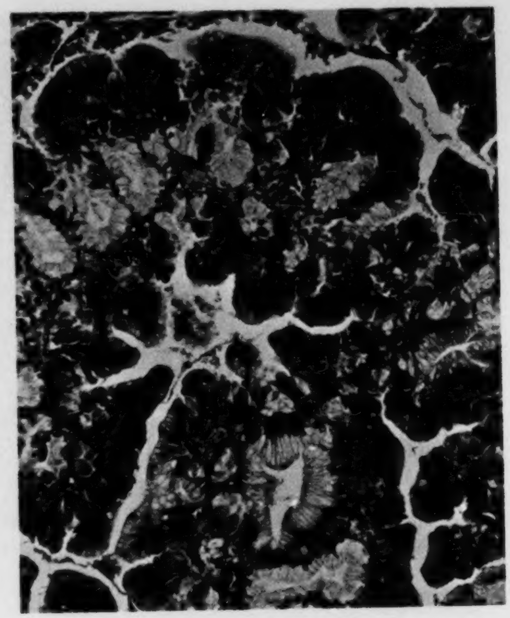

Figure 15
ADENOMA WITH PANETH CELLS
In this adenoma, the glands and small papillary structures are lined by mucus-secreting columnar cells and Paneth cells, which stain darker. X160.

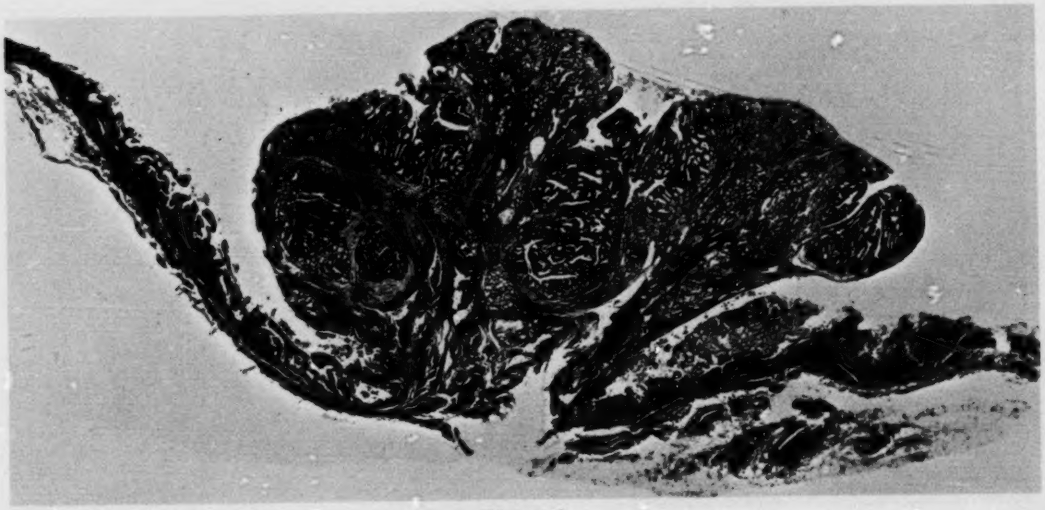

Figure 16
(Figures 16 and 17 from same patient)
TUBULAR ADENOMA WITH LOBULES
This whole mount section is through a small sessile tubular adenoma composed of lobules. X4.

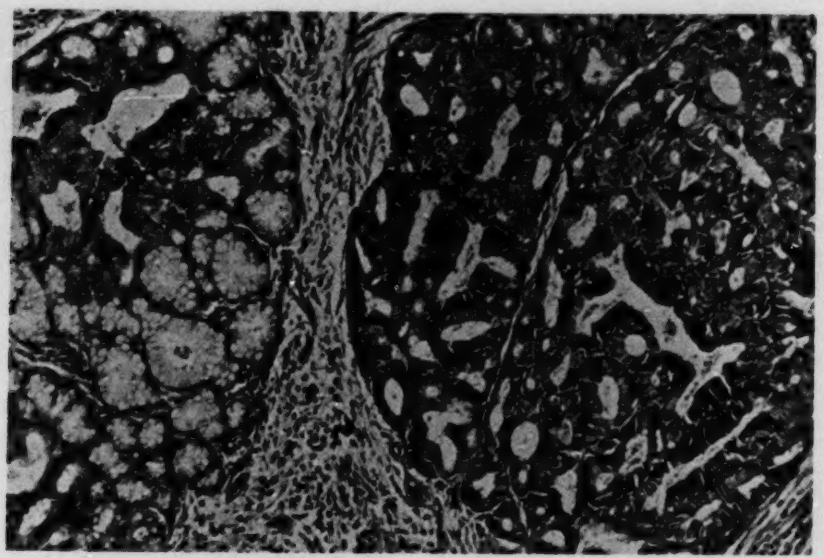

Figure 17
TUBULAR ADENOMA WITH LOBULES

Histologic section of the adenoma shown in figure 16. There are two well defined lobules separated by a band of connective tissue. One is composed of glands lined predominantly by mucus-secreting cells, while the other consists of glands lined by tall columnar epithelium devoid of mucin. X150.

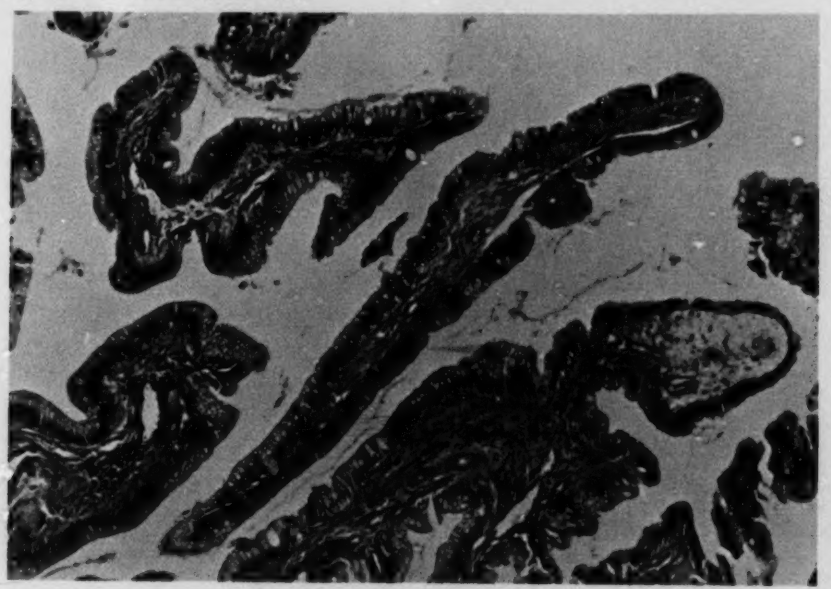

Figure 18
PAPILLARY ADENOMA

A papillary adenoma is composed of fibrovascular stalks that extend outward into the lumen of the gallbladder. They are lined by tall columnar mucus-secreting cells. X100.

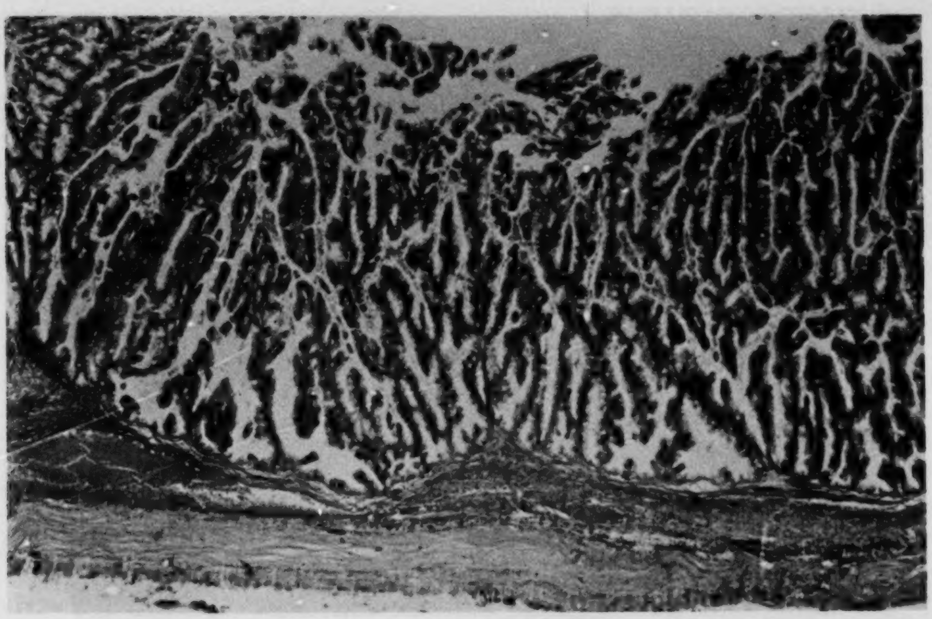

Figure 19
(Figures 19 and 20 from same patient)
PAPILLARY ADENOMA
Low power view of a papillary adenoma that resembles a villous adenoma of the large intestine. Multiple papillary projections, which frequently branch, extend outward from the wall of the gallbladder. X35.

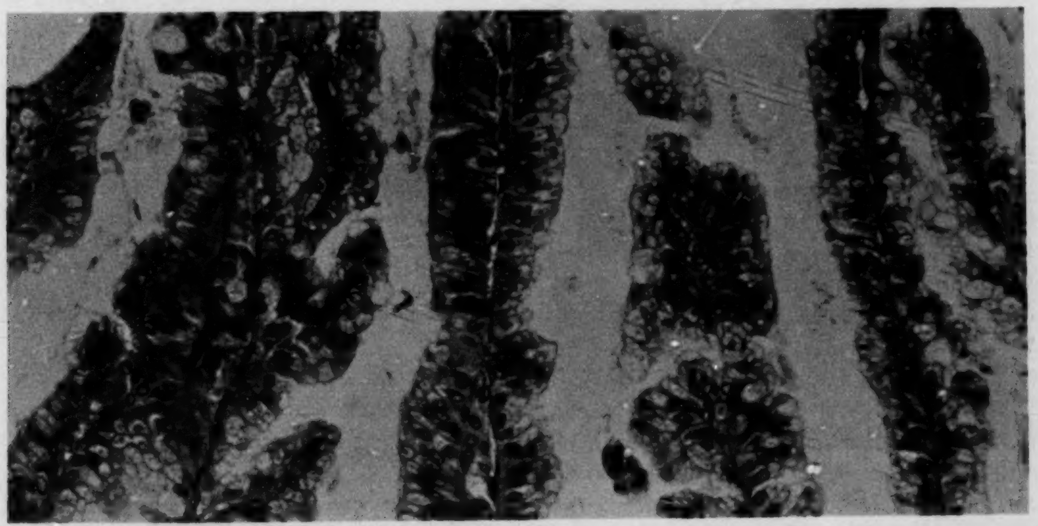

Figure 20
PAPILLARY ADENOMA
A high magnification of the tumor shown in figure 19. The papillary projections are lined by tall columnar cells that have bland nuclei and secrete mucus. X200.

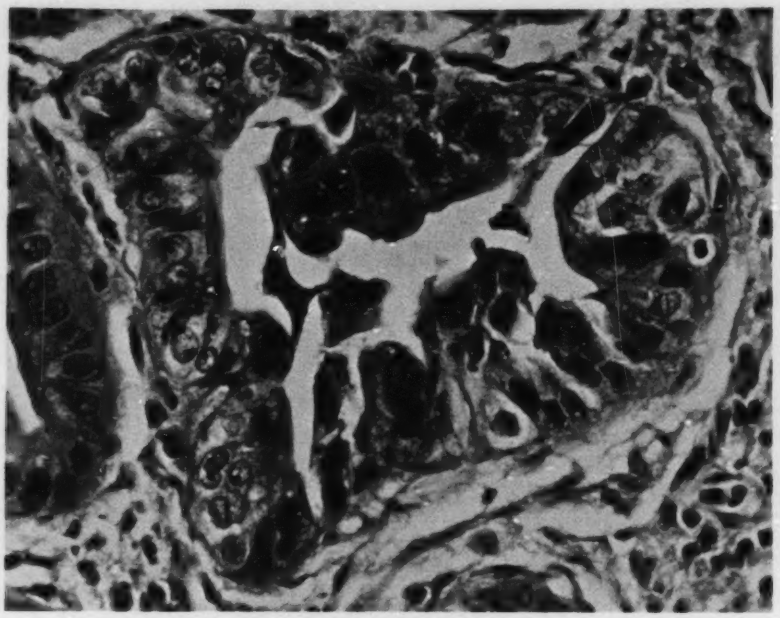

Figure 21
TUBULAR ADENOMA WITH CARCINOMA IN SITU
Marked cellular atypism and large hyperchromatic nuclei are seen in one gland. X530. (From Christensen, A.H. and Ishak, K.G. Benign tumors and pseudotumors of the gallbladder. Arch. Pathol. 90:423-432, 1970.)

adenomas arising in the gallbladder or bile ducts (Ochsner and Gage; Tabah and McNeer; fig. 21). Invasion of the stalk, however, has not been reported, and it is unlikely that adenomas are precancerous lesions that progress to invasive carcinoma. Despite an intentional search, we failed to find remnants of tubular or papillary adenomas in over 380 carcinomas of the gallbladder.

The differentiation of atypical changes from in situ or invasive carcinoma can be difficult, especially for pathologists who do not encounter many adenomas from the biliary tract. The histologic criteria for differentiation are similar to those used for adenomas arising in the intestine.

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Mixed Tumor

A lesion similar to a mixed tumor of the salivary glands has been reported in the gallbladder. It contained cartilage and duct-like structures in a fibromyxomatous stroma.

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BENIGN MESENCHYMAL TUMORS

Benign mesenchymal tumors of the gallbladder are seldom seen and do not differ in structure from those found in other organs. Leiomyomas, hemangiomas, and lipomas have been reported. They should not cause diagnostic problems. We have also seen a hyalinized leiomyoma and a lymphangioma of the gallbladder.

Multiple smooth muscle tumors occurring in many sites, including the gallbladder, were found in a four year old boy with a Wiskott-Aldrich-like syndrome (Huff et al.).

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PARAGANGLIOMA

This is an exceedingly rare lesion in the gallbladder. The only two reported examples were incidentally found in cholecystectomy specimens. Most likely, the tumor arises from the small paraganglia located in the perimuscular connective tissue. Grossly, it appears as a small nodule that protrudes from the external surface. Histologically, the characteristic "zell-ballen" pattern is observed (figs. 22, 23).

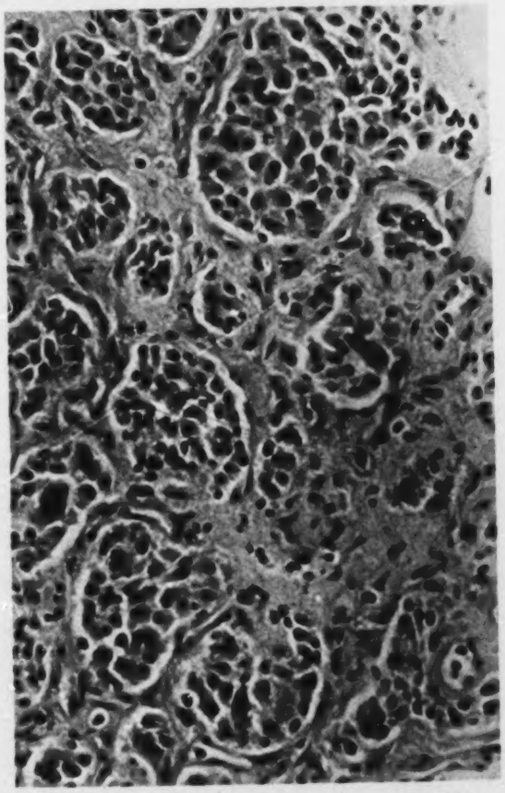

Figure 22
PARAGANGLIOMA
This tumor contains clusters of polygonal cells, some with large hyperchromatic nuclei. The clusters are separated by thin fibrous septae containing capillaries. X160. (Courtesy of Dr. H.D. Appelman, Ann Arbor, MI.)

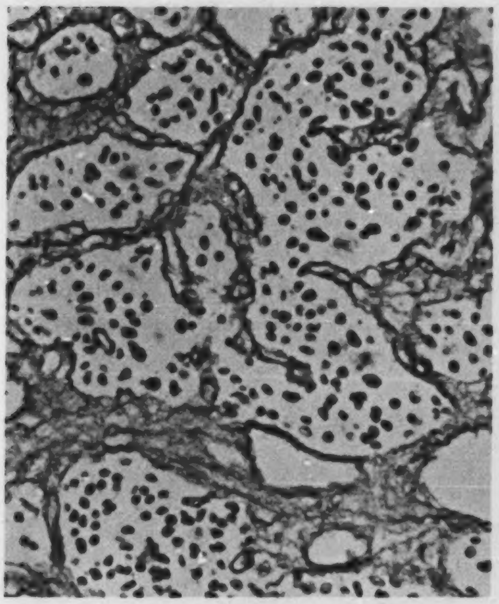

Figure 23
PARAGANGLIOMA
Reticulin stain showing "zell-ballen" pattern and intervening vascular septae. X200. (Courtesy of Dr. H.D. Appelman, Ann Arbor, MI.)

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TUMORS OF NERVES

A plexiform neurofibroma in the wall of the gallbladder is shown in figure 24. We have not been able to locate reports of gallbladder involvement in cases of neurofibromatosis.

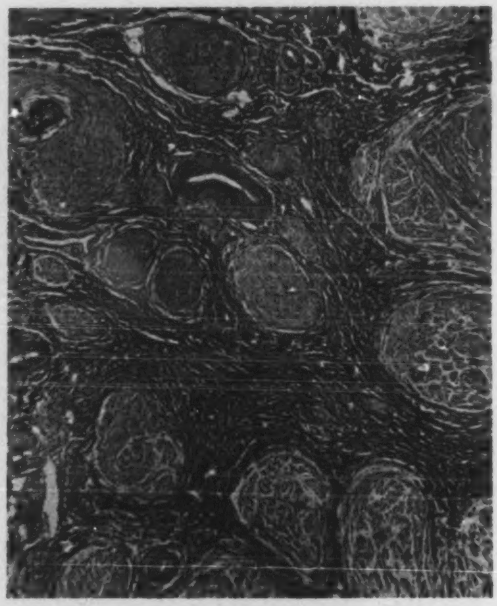

Figure 24
PLEXIFORM NEUROFIBROMA
A section through the gallbladder wall showing numerous hypertrophic and distorted nerve bundles characteristic of a plexiform neurofibroma. X60.

GANGLIONEUROFIBROMATOSIS

Ganglioneurofibromatosis of the gallbladder is found in some cases of the type 2b multiple endocrine neoplasia syndrome. The basic histologic changes, which are similar to those found in the small and large intestine, include Schwann cell and ganglion cell proliferation primarily in the lamina propria, as well as enlarged and distorted nerves with a plexiform appearance in the muscle layer and perimuscular connective tissue (figs. 25, 26). Lesions have been observed in children and in adults and may cause biliary tract symptoms.

Involvement of the gallbladder should be considered in patients who are known to have the syndrome and who develop symptoms related to the biliary tract.

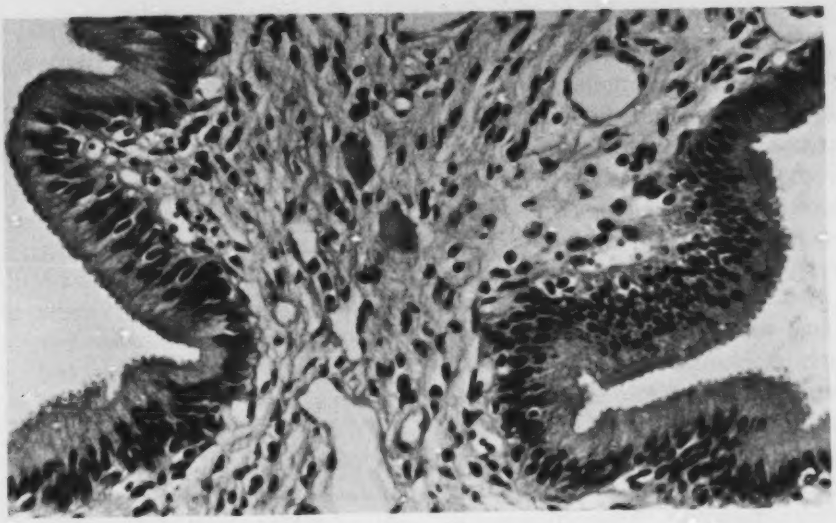

Figure 25
(Figures 25 and 26 from same patient)
GANGLIONEUROFIBROMATOSIS
Ganglioneurofibromatosis of the gallbladder. A small group of ganglion cells is visible in the lamina propria. X250. (Courtesy of Dr. M. Ibanez, Houston, TX.)

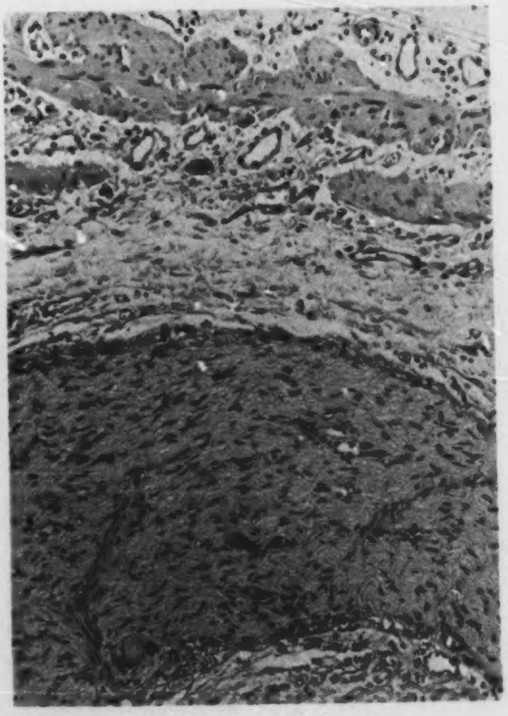

Figure 26
GANGLIONEUROFIBROMATOSIS
An enlarged nerve trunk is present in the perimuscular connective tissue. A few ganglion cells are also visible. X100. (Courtesy of Dr. M. Ibanez, Houston, TX.)

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MALIGNANT TUMORS OF THE GALLBLADDER

Although the gallbladder has a simple histologic structure, it gives rise to a wide variety of malignant tumors. Over 98 percent of such tumors are carcinomas that, in our opinion, result from the neoplastic transformation of the columnar lining epithelium. The other types, which are rare, include carcinosarcomas, rhabdomyosarcomas, and leiomyosarcomas.

According to their histologic differentiation, carcinomas can be classified into four types: adenocarcinoma; squamous cell carcinoma; adenosquamous carcinoma; and oat cell carcinoma (Table 1). Adenocarcinomas are further subclassified into well differentiated, papillary, intestinal, pleomorphic giant cell, signet ring cell, colloid, clear cell, and poorly differentiated small cell types. This classification is more detailed than the one published by the World Health Organization, which lists only three types — adenocarcinoma, squamous cell carcinoma, and undifferentiated carcinoma — and three variants — signet ring cell, adenosquamous, and mucinous carcinomas (Gibson and Sobin).

Since the gallbladder originates from the foregut, in the same region as the pancreas, we carefully considered the histologic types and terminology of exocrine pancreatic tumors in formulating this classification. Many tumors that arise in both sites are histologically similar, and we believe that a similar classification and nomenclature should be used for these tumors. (See the Fascicle on Tumors of the Exocrine Pancreas.)

Carcinomas of the gallbladder are not likely to cause diagnostic problems for the pathologist. Most tumors are adenocarcinomas, and many are histologically similar to adenocarcinomas that arise in other sites. Often, carcinomas will exhibit more than one histologic type; for example, patterns of a well differentiated and pleomorphic giant cell carcinoma may coexist in the same tumor. In tumors with more than one histologic pattern, the trend has been

Table 1

CLASSIFICATION OF MALIGNANT TUMORS OF THE GALLBLADDER

MALIGNANT EPITHELIAL TUMORS
- Adenocarcinoma
  - Well differentiated
  - Papillary
  - Intestinal type
  - Pleomorphic giant cell
  - Poorly-differentiated, small cell
  - Signet ring cell
  - Clear cell
  - Colloid
  - With choriocarcinoma-like areas
- Squamous cell carcinoma
- Adenosquamous carcinoma
- Oat cell carcinoma
- Others

MALIGNANT MESENCHYMAL TUMORS
- Embryonal rhabdomyosarcoma (sarcoma botryoides)
- Leiomyosarcoma
- Malignant fibrous histiocytoma
- Angiosarcoma
- Kaposi's sarcoma
- Others

MISCELLANEOUS
- Carcinosarcoma
- Carcinoid tumor
- Malignant lymphoma
- Malignant melanoma
- Others

to classify them according to the predominant pattern. However, since knowledge about the natural history of these tumors is incomplete and the response of the different histologic components to therapy not well known, we recommend that the pathologist list all patterns in his final diagnosis. Unfortunately, because of a lack of consistency in classification, it is difficult to determine whether certain types are associated with a better prognosis. Clinical pathologic studies on gallbladder cancer are limited because the disease is often diagnosed late in its course.

Table 2 shows the different histologic types in our series of 386 cases collected over a 20-year period. Well differentiated and pleomorphic giant cell adenocarcinomas were the most common, together comprising 61 percent, while squamous cell and signet ring cell carcinomas were uncommon.

Because gallbladder carcinoma often displays a spectrum of histologic patterns, we can question the clinical significance of subclassification, especially when many patients die shortly after diagnosis (Vadheim et al.; Donaldson and Busuttil). However, there are data which suggest that subclassification is justified in most cases. A comparison of the histologic types in our series with those in others is difficult since different classifications were used. But in the few studies in which this comparison can be made (Vaittinen; Shieh et al.), it seems that anaplastic carcinomas, including small and giant cell types and adenosquamous carcinomas, are proportionally more common in geographic areas where there is a high incidence of gallbladder carcinoma. Clinically, papillary carcinomas have a better prognosis than other types and should obviously be separated. Oat cell

Table 2

DISTRIBUTION OF HISTOLOGIC TYPES IN 386 PATIENTS WITH MALIGNANT TUMORS OF THE GALLBLADDER

Histologic Type	Number of Patients	Sex Distribution	
		Males	Females
Adenocarcinoma, well differentiated	186 (48.2)*	31	155
Pleomorphic giant cell adenocarcinoma	51 (13.2)	14	37
Adenosquamous carcinoma	37 (9.58)	2	35
Poorly-differentiated adenocarcinoma, small cell type	25 (6.48)	3	22
Oat cell carcinoma	18 (4.66)	2	16
Papillary adenocarcinoma	17 (4.40)	1	16
Colloid carcinoma	16 (4.14)	5	11
Carcinoma in situ	14 (3.63)	1	13
Signet ring cell carcinoma	10 (2.59)	3	7
Squamous cell carcinoma	4 (1.04)	1	3
Intestinal type adenocarcinoma	4 (1.04)	1	3
Adenocarcinoma with choriocarcinoma-like areas	1 (0.26)	0	1
Carcinosarcoma	1 (0.26)	0	1
Carcinoid tumor	1 (0.26)	1	0
Malignant fibrous histiocytoma	1 (0.26)	0	1
Total	386	65	321

*Percentage in parentheses

carcinomas, which are histologically and probably histogenically different from adenocarcinomas, can give rise to endocrine syndromes, such as Cushing's syndrome, and for this reason should be correctly diagnosed. A more important reason for separation is that the chemotherapeutic approach to oat cell carcinoma differs from adenocarcinoma.

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EPIDEMIOLOGY

Cancer of the gallbladder is uncommon among the white and black races. In the United States, the incidence rate is approximately 1 per 100,000 in males and 2 per 100,000 in females, accounting for 0.3 percent of all cancers in males and 0.7 percent in females (Table 3). The incidence rate of extrahepatic bile duct cancer, including the ampulla, is 1.5 for males and 1.0 for females, which accounts for 0.5 percent of all cancers in males and 0.4 percent in females.

These incidence figures, determined by tumor registration, are similar to those based on autopsy reviews. From a total of 206,098 autopsy cases published in 1949, there were 908 carcinomas of the gallbladder (0.43 percent), and in 46,480 surgical operations, 569 gallbladder cancers (1.22 percent) were found (Arminski). In a smaller series of 13,330 autopsies, 55 cases of gallbladder cancer were encountered,

Table 3

INCIDENCE RATES IN THE UNITED STATES
FOR CANCERS OF THE GALLBLADDER AND EXTRAHEPATIC BILE DUCTS

		Gallbladder Cancer (ICD-O: 156.0)		Extrahepatic Bile Duct Cancer[a] (ICD-O: 156.1 – 156.9)	
		Rates[b]	Percent	Rates[b]	Percent
Male	1969–1971[c]	1.1	0.3	1.5	0.5
	1973–1977[d]	1.0	0.3	1.6	0.4
Female	1969–1971[c]	2.1	0.8	1.0	0.4
	1973–1977[d]	1.8	0.6	1.1	0.4

[a] Includes tumors at Ampulla of Vater
[b] Per 100,000 population
[c] Data from Third National Cancer Survey 1969–1971
[d] Data from Surveillance, Epidemiology, and End Results, NCI, 1973–1977

which represented 0.41 percent of all autopsies and 3.0 percent of all cancers (Kirshbaum and Kozoll). In the same series, 62 cases (0.46 percent) of extrahepatic bile duct cancer were discovered.

In American Indians, the incidence rate is much higher. In New Mexico, for instance, the rates are 5.1 per 100,000 for Indian males and 21.1 for Indian females, compared with 0.8 for white males and 1.4 for white females. Spanish descendents living in the same area have intermediate rates, 2.0 for males and 10.5 for females (Morris et al.). Clinically, cancers of the gallbladder and extrahepatic bile ducts are found in 5.4 percent of all biliary tract operations among Southwestern American Indians. These cancers are the most common intestinal neoplasm in this population and the third most common malignancy in female American Indians (Rudolph et al.).

Some of the lowest rates are seen in blacks in the United States and Africa (Fraumeni). According to the Third National Cancer Survey, the annual age adjusted incidence rate for gallbladder cancer in American blacks is 0.7 for males and 1.6 for females; for extrahepatic bile duct cancer, the rate is 1.2 for males and 0.8 for females.

Regional variation in mortality resulting from biliary tract cancer has been observed in the United States (Fraumeni). Increased mortality is seen in the southwest, north-central region, and Appalachia. While the cluster in the southwest can be explained by the Indian and Hispanic composition of the population, there is no clear explanation for the clusters in the north-central region or Appalachia.

In England and Wales, the incidence of carcinoma of the gallbladder is similar to that in the United States (Cooke et al.). According to the Birmingham, England, Regional Cancer Registry, the rates for cancer of the gallbladder and bile ducts combined are 1.7 for males and 3.0 for females (Waterhouse).

High rates of cancer of the gallbladder are also found in Latin America and in countries in central and eastern Europe (Waterhouse et al.). In Santiago, Chile, for instance, the rate in women in 9.0 per 100,000 (Puffer and Griffith).

The high rate of gallbladder cancer observed in Mexico, 8.5 per 100,000 women, is also found in Mexican Americans (Menck et al.). In the Los Angeles area, carcinoma of the gallbladder is the third most common type of malignant tumor in Mexican American women (Steiner).

Other countries have reported the incidence of gallbladder cancer. In Israel, for example, the rate is 1.1 among males and 5.2 among females (Hart et al.). The incidence is greater in females born in Europe than those born in Asia or Africa. No such differences exist among males. Although population based incidence figures are not available for Brazil, neoplasms of the gallbladder account for 0.5 percent of all cancers in females and 0.1 percent in males. Cancers of the extrahepatic bile ducts comprise 0.1 percent of all malignancies in males and females (Torloni and Brumini). The incidence rate per 100,000 in two large cities in Brazil, Recife and Sao Paulo, is 1.0 for males and 2.3 for females and 1.4 for males and 2.9 for females, respectively (Waterhouse et al.).

Other epidemiologic characteristics are shown in Table 4. Approximately 16 percent of gallbladder carcinomas are found incidentally during examination of the specimen following cholecystectomy.

Table 4

SUMMARY OF SOME DIFFERENCES IN THE EPIDEMIOLOGIC FEATURES OF GALLBLADDER AND EXTRAHEPATIC BILE DUCT CANCER*

	Gallbladder	Biliary Tract
Total Cases	697	470
Average Age	64.8	63.3
Males: Females	1:3.4	1:1
Incidence of Cholelithiasis	75%	32%
Incidentally Found at Operation	16%	–

*From Soloway, R.D., Balistreri, W.F., and Trotman, B.W. The Gallbladder and Biliary Tract. In: Recent Advances in Gastroenterology, No. 4. New York: Churchill Livingstone, 1980.

SEX AND AGE DISTRIBUTION

In general, females with gallbladder cancer outnumber males 3:1, although this varies from 2:1 to 5:1 in different areas of the world. In contrast, extrahepatic bile duct cancer shows no significant sex association, although the disease is often reported to be more common in males (Table 3). Female patients with gallbladder carcinoma are often multiparous.

Cancer of the biliary tract is a disease of older age groups (figs. 27, 28). For extrahepatic bile duct cancer, the peak age is in the range 65-69 years and for gallbladder cancer, 70-79 years. The peak age for males occurs five years earlier for gallbladder cancer and 10 years earlier for extrahepatic bile duct cancer than for females (figs. 27, 28). Carcinoma of the gallbladder was found in an 11 year old American Indian girl, the youngest case on record (Rudolph and Cohen).

Since cancer of the biliary tract occurs primarily in older age groups, the incidence of carcinoma discovered in patients undergoing surgery for biliary tract disease will increase with age (Table 5). Approximately 10 percent of patients 65 years or older with biliary tract disease can be expected to have carcinoma of the gallbladder or bile ducts (Glenn and Hays; Glenn and Hill).

Table 5

AGE FACTOR IN THE INCIDENCE OF CANCER ENCOUNTERED IN OPERATIONS FOR BILIARY TRACT DISEASE*

	AGE GROUP			
	<50	50-64	65-74	≥75
Total operative cases of biliary tract diseases	2395	1478	339	59
Cancers of gallbladder or extrahepatic bile ducts	6	46	31	7
Percent of cases with cancer	0.25	3.1	9.1	11.9

*Not including ampullary lesions. (From Glenn, F. and Hill, M.R., Jr. Extrahepatic biliary-tract cancer. Cancer 8:1218-1225, 1955.)

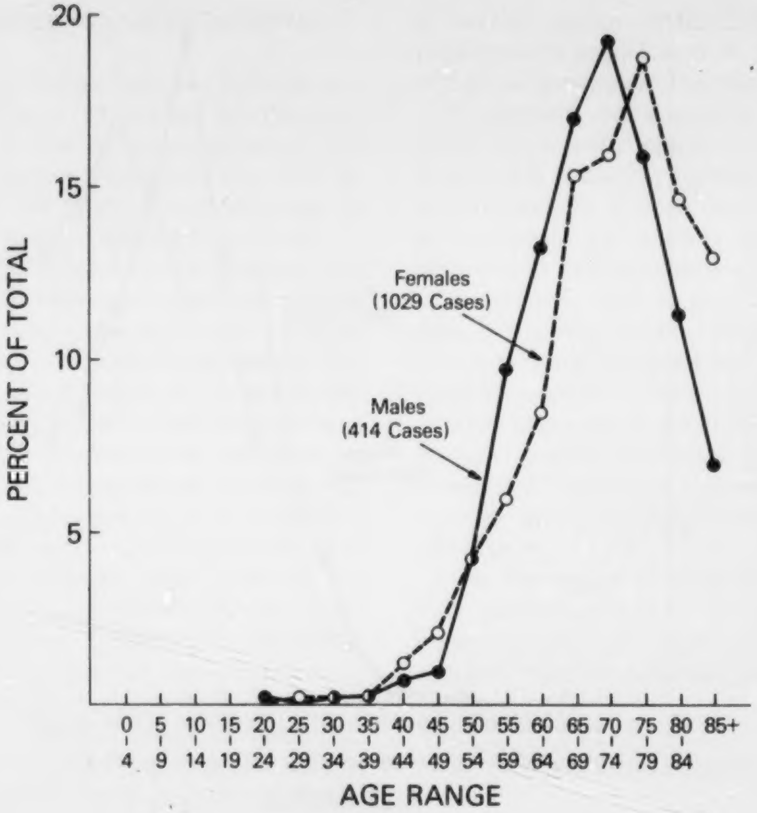

Figure 27
AGE DISTRIBUTION
GALLBLADDER CANCER
Age distribution for cancer of the gallbladder in the Third National Cancer Survey, 1969-1971. The data are corrected for the age distribution of the population.

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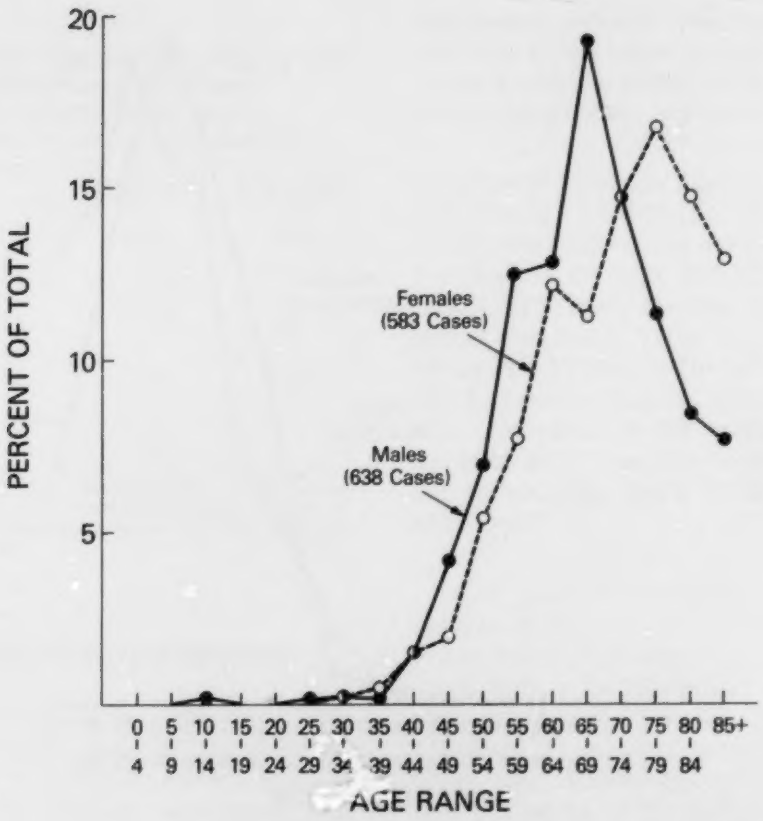

Figure 28
AGE DISTRIBUTION
EXTRAHEPATIC BILE DUCT CANCER
Age distribution for cancer of the extrahepatic bile ducts according to the Third National Cancer Survey, 1969-1971. The data are corrected for the age distribution of the population.

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CLINICAL MANIFESTATIONS

There is a marked contrast between the symptomatology of cancer of the gallbladder and that of the extrahepatic bile ducts. As in other sites, the clinical findings depend on the physical encroachment of an enlarging tumor on vital structures.

Gallbladder cancer usually presents late in its course, after the tumor has spread, while extrahepatic bile duct cancer presents early, primarily because of obstruction. The symptoms of gallbladder cancer are usually delayed because the tumor develops in a small organ with a blind end and does not interfere with the flow of bile. Furthermore, the signs and symptoms of a preexisting cholecystitis, which are found in 50 to 90 percent of patients, may mislead the physician and cause a delay in diagnosis.

The signs and symptoms of gallbladder cancer are not specific, often resembling those of chronic cholecystitis (Bismuth and Malt). Pain, which usually is the initial complaint, occurs in 75 percent of cases. It may be intermittent or persistent, severe, and, for the most part, localized in the right upper quadrant. There is often a palpable mass, hepatomegaly, and eventually jaundice, nausea, vomiting, anorexia, and weight loss (Hamrick et al.). Pruritus usually occurs with jaundice.

Thirty to 60 percent of patients develop jaundice, usually as a result of obstruction from the tumor extending to the cystic and common duct, or less often caused by metastases in the liver. It is a poor prognostic sign, since 85 percent of patients with jaundice have nonresectable lesions at the time of diagnosis (Gradisar and Kelly). In addition to patients with jaundice, resection is usually not possible in patients with enlarged liver, palpable abdominal masses, or ascites. About 20 percent of patients present with ascites and 10 percent with duodenal obstruction (Pemberton et al.).

In contrast, the dominant and usually initial sign of extrahepatic bile duct cancer is jaundice, occurring in more than 90 percent of patients. The jaundice can progress or fluctuate, but usually occurs before widespread tumor dissemination.

In addition, there is pain, mostly localized in the epigastrium, less frequently in the right upper quadrant as in the case of gallbladder cancer. The pain, which occurs in 50 to 70 percent of patients, may be intermittent, colicky, or constant. Nonspecific symptoms eventually appear, such as nausea, fever, and various gastrointestinal complaints.

The first signs of local recurrence for both gallbladder and extrahepatic bile duct cancer include right upper quadrant pain, a palpable mass, an enlarged liver, back pain, and jaundice.

Systemic Manifestations

In addition to the common signs and symptoms of biliary tract cancer, there are cases with a remote or systemic presentation. These cases are rare and should be included among the paraneoplastic syndromes.

In one patient, carcinoma of the gallbladder was associated with Cushing's syndrome, the result of excess production of ACTH by the tumor, which was reported as an APUDoma (Spence and Burns-Cox). In other patients, carcinoma of the gallbladder has been associated with acanthosis nigricans (Werko), bullous-type pemphigoid skin lesions (Post et al.) and the Zollinger-Ellison syndrome, which was caused by a malignant G cell tumor of the gallbladder (Nakamura et al.). The latter case is of some interest, since G cells have recently been described in the human gallbladder with intestinal metaplasia. We have also seen an oat cell carcinoma of the gallbladder that gave rise to Cushing's syndrome.

Carcinoma of the extrahepatic ducts associated with the Leser-Trelat sign (rapid growth of multiple seborrheic keratoses accompanied by pruritus) and pure red blood cell aplasia has been reported in a patient with ulcerative colitis (Lee et al.). Recently, a carcinoma of the gallbladder was also associated with the Leser-Trelat sign (Jacobs and Rigel). It has been suggested that the Leser-Trelat sign results from the secretion by the tumor of a small peptide similar to the skin growth factor (Jacobs and Rigel).

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LABORATORY FINDINGS

Laboratory findings are not diagnostic. Jaundice in patients with carcinoma of the gallbladder or extrahepatic ducts usually indicates an extrahepatic obstruction and is manifested by hyperbilirubinemia, bilirubinuria and elevated levels of serum alkaline phosphatase, 5′ nucleotidase, and leucine aminopeptidase. These changes are not specific for carcinoma, but are associated with extrahepatic bile duct obstruction from many causes.

In patients who are not jaundiced but complain of pain, indigestion, or other symptoms, laboratory findings are either normal or show nonspecific changes. Serum levels of alanine aminotransferase and lactic acid dehydrogenase may be elevated, especially with liver involvement or cholestasis. Normal values do not, however, exclude metastatic lesions in the liver.

Other laboratory observations have been reported, although their usefulness remains to be evaluated. Carcinoma of the extrahepatic biliary tree produces an increase in both the serum and bile levels of CEA, but since similar levels may also occur in biliary obstruction from other causes, a rise may not indicate malignancy (Tatsuta et al.). Carcinoma of the gallbladder has been associated with elevated levels of serum haptoglobin (Hudson and Enck) and serum alpha-fetoprotein (Kim et al.).

In 90 to 95 percent of cases, a carcinomatous gallbladder is nonfunctional and does not visualize during oral cholecystography. Visualization, however, does not exclude carcinoma, since in some cases the gallbladder remains functional and may even show a filling defect (Rabinov).

Endoscopic retrograde cholangiography (Silvis et al.), ultrasonography (Dalla Palma et al.), and computed tomography are proving useful in the diagnosis of cancers of the gallbladder and bile ducts (see p. 124). In one report, 20 of 27 patients with carcinoma of the gallbladder were correctly diagnosed by computed tomography (Itai et al.). Diagnosis can also be made by angiography which depends on the demonstration of neovascularization (Abrams et al.).

Most cases of carcinoma are diagnosed during exploratory laparotomy or during surgery for cholelithiasis or some obstructive lesion.

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CARCINOEMBRYONIC ANTIGEN (CEA)

As an endodermal derivative, the biliary tract should contain many substances that are also found in the intestine. For instance, normal bile contains at least three CEA-related macromolecules, which have been designated biliary tract glycoproteins I, II, and III (Svenberg). Type 1, which occurs in normal bile, is similar to CEA but lacks the tumor-associated antigenic determinants. It is found in all epithelium throughout the biliary tract, including the bile canaliculi (Svenberg et al.). In inflammatory conditions, type I is replaced by types II and III, the latter of which is immunologically identical to CEA. Because of continuing research on CEA and biliary glycoproteins, we can expect that the terminology will change and that our concepts of their structure and function will need revision.

In patients with carcinoma of the biliary tract, the serum levels of CEA increase. However, since serum levels also increase with other obstructive or inflammatory conditions, their value in the differential diagnosis of cancer is questionable (Lurie et al.). Similarly, CEA levels in the bile also increase in patients with biliary cancer. However, the CEA titers in bile alone cannot be used in the differential diagnosis of biliary cancer, since CEA levels also increase with obstructive inflammatory conditions and with other malignancies in the region, for example, head of the pancreas.

With immunohistologic technics, we have demonstrated a variable content of CEA, or a CEA-related substance, in different tumor types (Albores-Saavedra et al., 1983). Differentiated adenocarcinomas usually contain abundant CEA, whereas the poorly differentiated adenocarcinomas, including the pleomorphic giant cell and small cell types, have much less. About 25 percent of pure oat cell carcinomas contain focal areas of CEA positive cells (Albores-Saavedra et al., 1984). CEA is also found in the glandular component of the combined form of these tumors.

In normal gallbladder epithelium, a small amount of CEA can usually be detected even in formalin fixed material. The CEA occurs in focal areas as linear staining along the apical cytoplasmic border. However, the staining never reaches the intensity seen in malignant tumors. A similar focal distribution of CEA is also found in normal colonic epithelium.

It is doubtful that CEA will ever play an important role in the histologic diagnosis of gallbladder or bile duct cancer. Perhaps it may be used to differentiate certain epithelial tumors from malignant mesenchymal tumors, such as pleomorphic giant cell carcinomas from sarcomas. Nevertheless, according to available data, the distribution of CEA in normal gallbladder epithelium and in carcinomas of the gallbladder follows the same pattern observed in the colon.

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ETIOLOGIC CONSIDERATIONS

The etiology of gallbladder cancer and bile duct cancer are considered together.

Genetic

As discussed under "Epidemiology," cancer of the gallbladder is concentrated in certain racial and ethnic groups. Unusually high rates are found among American Indians and Hispanic Americans, especially those living in Arizona and California, and among South and Central American Indians. The Hispanic Americans, it should be recalled, are descendants of the early Spanish settlers and have an ethnic background of both American Indian and Spanish.

Epidemiologic studies have suggested that among American Indians there is a genetic predisposition for carcinoma of the gallbladder and for biliary tract disease in general (Devor and Buechley). Familial aggregations of gallbladder cancer have been observed in the United States (Devor and Buechley) and in other countries (Trajber et al.).

The high incidence of carcinoma of the gallbladder in Hispanic Americans seems to be the result of racial intermixture, since the Iberian Spaniards, the historical source of New Mexico's original settlers, do not have high rates of gallbladder cancer – 2.7/100,000 for females and 1.8/100,000 for males (Devor and Buechley). Studies of Hispanics in Colorado indicate that the Indian contribution to the gene pool is as high as 40 percent. It is possible, therefore, that the high rates observed in some countries in Latin America may also be the result of racial intermixture between the Spanish immigrants and native American Indians.

The incidence of cancer of the gallbladder in other Hispanic groups, such as the Puerto Ricans and Cubans who have a different ethnic background, is 1.9 per 100,000, which is the same as that in the United States. In general, countries in Latin America with a large Indian population during the Spanish migration have higher rates of gallbladder cancer than countries which did not have a large Indian population.

Gallstones

The association of carcinoma of the gallbladder with gallstones has been known since 1861. Found in over 80 percent of patients, this association is accepted by many as indicating a causal relationship and is the reason for the widely held view that elective cholecystectomy for cholelithiasis is a preventive measure for gallbladder cancer (Graham; Hart et al.). In considering all age groups, the overall incidence of carcinoma of the gallbladder in all patients with cholelithiasis is 0.5 to 3 percent. In contrast, tumors of the extrahepatic bile ducts are usually not associated with cholelithiasis or choledocholithiasis.

The possible etiologic relationship of gallstones to carcinoma of the gallbladder is strengthened by other observations. There is a higher incidence of carcinoma in females, who have a higher incidence of gallstones than males. Gallstones are more common in the gallbladder than in the bile ducts, and gallbladder cancer is more common than bile duct cancer. Finally, the incidence of carcinoma is higher in ethnic groups such as American Indians, who have a high incidence of stones, and is low in ethnic groups such as American blacks, who have a low incidence of stones.

Although the relationship of cholelithiasis to carcinoma is not understood, most assume that chronic irritatioh promotes neoplastic transformation. This assumption has some support, because epithelium from lithiferous gallbladders incorporates tritiated thymidine 23 times greater than normal (Putz and Willems). Biochemical studies have indicated that stones from cancer patients are formed through standard mechanisms for cholesterol precipitation and not secondary to stasis or infection. It should be noted that carcinomas of the gallbladder are usually associated with cholesterol-type stones.

Composition of Bile and Gallstones

In considering the etiology of carcinoma of the gallbladder, we should note that the composition of bile and gallstones is not uniform in all parts of the world. In La Paz, Bolivia, for example, a city with a fivefold increase in the incidence of carcinoma of the gallbladder compared to that in the United States, only cholesterol stones were found in 138 patients who were studied (Soloway et al.). This is in contrast to Philadelphia, an area with a low incidence of gallbladder cancer, where 27 percent of patients undergoing cholecystectomy have pigment gallstones (Trotman et al.). The stones from Bolivia contain a much higher proportion of cholesterol and therefore much less calcium bilirubinate, calcium carbonate, and other noncholesterol components than stones from Philadelphia. In Bolivia, the Caucasians, Mestizos, and Indians have a uniform stone composition, with the cholesterol content greater than 90 percent. This also includes patients with carcinoma of the gallbladder.

Bile obtained from Bolivian patients without cholelithiasis during abdominal surgery resembles bile from patients in the United States, except that it is less saturated with cholesterol. Patients with cholelithiasis in the United States have bile with a similar concentration of bile salts and phospholipids, but an increased concentration of cholesterol, causing the bile to be supersaturated with cholesterol, which is a prerequisite for cholesterol stone formation in the United States. In contrast, patients in Bolivia who have gallstones, or gallstones and carcinoma, have bile that contains significantly less bile salts, phospholipids, and cholesterol. Furthermore, bile from these patients is undersaturated with cholesterol despite the formation of cholesterol gallstones (Rios-Dalenz et al.). This suggests that factors other than cholesterol saturation are important for the formation of cholesterol gallstones in this population and that these factors may be similar to the ones predisposing to the development of carcinoma of the gallbladder.

Taurine and glycine conjugates of lithocholic acid are increased in all gallstones examined in the United States and Bolivia. However, conjugates of lithocholic acid are also increased in the bile from patients in Bolivia. This increase occurs in patients with cholelithiasis with or without carcinoma. The reason for this increased proportion of lithocholic acid, a known cocarcinogen (Narisawa et al.), in the bile of Bolivian patients is not known. Patients in Bolivia with cholelithiasis, with or without carcinoma, are able to sulfate only 25 to 35 percent of their lithocholic acid, whereas control patients in Bolivia and patients in the United States can sulfate 95 to 100 percent of the lithocholic acid. Thus, the results suggest that some Bolivians are not protected from the toxicity of lithocholic acid because they cannot completely sulfate the bile acid in the liver.

An analysis of gallstones from Mexico reveals that patients with carcinoma can also have calcium bilirubinate-palmitate pigment stones, a type of stone associated with stasis and infection in Japan. Most of the stones from Mexican patients, however, are cholesterol in type.

Congenital Cysts

A condition that predisposes to extrahepatic bile duct carcinoma is congenital cystic dilatation or choledochal cyst (Flanigan). Based on case reports, it has been estimated that the incidence of carcinoma in choledochal cysts is 20 times greater than the incidence of bile duct carcinoma in the general population. Adenocarcinomas are usually found in these cysts, although a case of sarcoma botryoides has been reported (Tsuchiya et al.). A mixture of bile and gastroduodenal contents may promote the development of carcinoma, since 50 percent of reported cases developed carcinoma after a mean interval of four years following internal drainage of the cyst (Flanigan). In fact, it has been claimed that those congenital defects in which the epithelium is in contact with bile — namely, congenital hepatic fibrosis, cystic dilatation of intrahepatic bile ducts, and choledochal cysts — have a greater risk for malignant transformation than defects not in contact with bile (Bloustein). Choledochal cysts are further discussed on page 181.

Calcification

Another condition predisposing to carcinoma is diffuse calcification, or porcelain gallbladder, as the lesion is often described.

Occurring in less than 0.1 percent of cholecystectomy specimens, diffuse calcification is associated with a carcinoma in 10 to 25 percent of cases (Berk et al.). Although the pathogenesis of the calcification has not been clarified, it is considered by many to be the end stage of a longstanding inflammatory process (Polk). It has also been suggested that calcium salts precipitate in the mucosa following obstruction of the cystic duct, usually by a gallstone, and exclusion of bile from the gallbladder (Phemister et al.). Ninety-five percent of patients have gallstones. Histologically, the calcification may involve the muscle layer or the mucosa and underlying lamina propria (Ochsner and Carrera).

The reason for the increased incidence of cancer in this condition is unknown. We suggest, however, that it may be related to the phenomenon of scar cancer, since there is usually fibrosis in addition to the calcification. For the most part, the tumors are infiltrating adenocarcinomas, although mucinous and squamous cell carcinomas have also been reported.

Infections

It has been reported that chronic carriers of Salmonella typhi die of hepatobiliary cancer six times as often as matched controls (Welton et al.). From this observation, it was suggested that salmonella surviving in the gallbladder produce altered bile salts that are carcinogenic. In one case, carcinoma of the gallbladder developed 67 years after the diagnosis of typhoid cholecystitis (Axelrod et al.). This relationship raises the possibility that other bacterial infections in the gallbladder may be important in the pathogenesis of carcinoma.

When careful culture technic is used, bile from patients with normal gallbladders is consistently sterile (Csendes et al.). In patients with chronic cholecystitis associated with cholesterol or pigment stones, the incidence of positive cultures is less than 33 percent and approaches 10 percent in the United States (Csendes et al.; Goodhart et al.; Lou et al.). In patients with acute cholecystitis, the incidence of infection increases to 60 percent.

Bacteria can be recovered from bile, stones, and the wall of the gallbladder. The types of bacteria usually found are mixtures of intestinal flora and include aerobic and anaerobic species (Shimada et al.; England and Rosenblatt). Anaerobic infection does not occur in the absence of aerobic organisms. Because of their labyrinthine interstices, gallstones, once infected, are unlikely to be sterilized by systemic antibiotics, even though some of these drugs are concentrated in bile.

In the Orient, infection, especially with E. coli, is the rule among patients with calcium bilirubinate stones (Maki). These stones, which contain calcium salts of bilirubin and fatty acids, are thought to form following bacterial deconjugation of bilirubin diglucuronide to bilirubin and bacterial lysis of phospholipid lecithin to lysolecithin and free fatty acids. These patients are subject to recurrent stone formation and chronic pyogenic cholangitis and cholangiohepatitis, but they do not have an increased incidence of extrahepatic biliary cancer.

It has been known for years that infestation with Clonorchis sinensis or Opisthorchis viverrini, conditions more prevalent in the Far East, is associated with carcinoma of the intrahepatic bile ducts (Hou). These infestations usually cause a chronic inflammatory reaction with proliferation of bile ducts. Recently, Clonorchis sinensis infestation has also been associated with carcinoma of the extrahepatic bile ducts (Koo et al.).

Occupation

Cancer of the biliary tract has been associated with exposure to chemicals used in the rubber industry (Mancuso and Brennan). However, the number of reported cases is small, and this association should be further studied. An excess risk for cancers of the intra- and extrahepatic bile ducts has been reported in workers in the nonelectrical machinery and primary metal industries (Houten and Sonnesso). In a remarkable case, asbestos bodies were found within a squamous cell carcinoma that developed in the cystic duct of a patient with an occupational exposure to asbestos (Szendroi et al.).

Drugs

In patients with carcinoma of the intrahepatic ducts, a higher than expected prevalence of methyldopa therapy was found (Broden and Bengtsson). Although mostly excreted in the urine, methyldopa passes through the enterohepatic circulation and is known to cause hepatitis and other adverse liver reactions.

Cases of biliary tract carcinoma associated with oral contraceptives (Ellis et al.) and isoniazid therapy have also been reported (Lowenfels and Norman). However, except for esophageal cancer in males, no differences were found in mortality from all cancers and cancer in individual sites in 41,226 tuberculous patients treated with isoniazid, compared to 22,811 patients not treated with isoniazid (Howe et al.).

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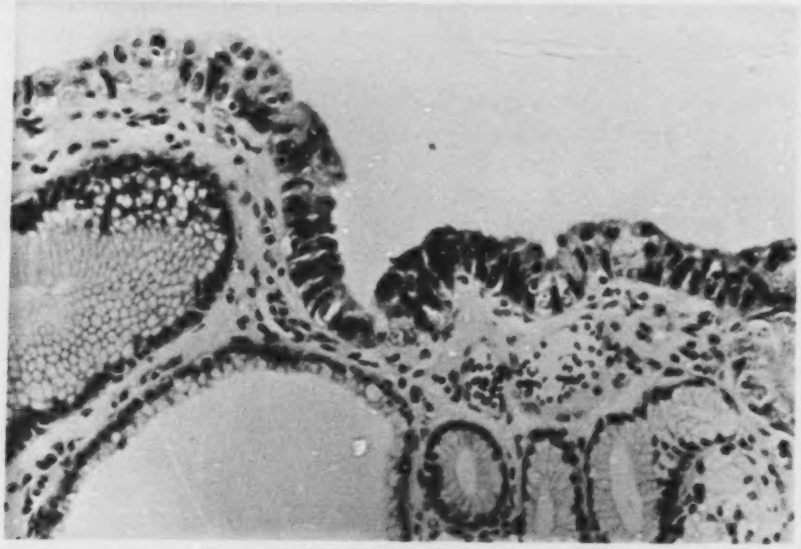
TUMORS IN ANIMALS

Spontaneous cancer of the extrahepatic biliary system rarely occurs in laboratory or domesticated animals. The highest natural incidence seems to be in bears. There are now several reports of extrahepatic biliary carcinoma occurring in tropical bears held in zoos in the United States and Europe (Dorn; Montali et al.).

Although gallbladder cancer has been produced in laboratory animals, experimental studies have not significantly contributed to our understanding of the disease. Early investigators, basing their work on the belief that chronic irritation was a cause, implanted gallstones, glass beads, pitch, and other substances in the gallbladders of laboratory animals in an effort to induce cancer, with limited success. Better results were obtained by implanting pellets of methylcholanthrene in the gallbladders of cats (Fortner). Gallbladder cancer was induced in hamsters by feeding dimethylnitrosamine and inserting cholesterol pellets into the gallbladder (Kowalewski and Todd). Other known carcinogens such as O-aminoazotoluene and N-methyl-N-formylhydrazine can induce biliary tract cancer as well as tumors in other sites in laboratory animals (Toth and Patil). Dogs fed aramite, an insecticide, for long periods developed gallbladder and bile duct carcinomas (Sternberg et al.).

Spontaneously occurring carcinomas of the gallbladder were found in two inbred strains of guinea pigs and in one random bred stock (Hoch-Ligeti et al.). Irradiation of these guinea pigs increased the incidence of tumors and metastases. This is of interest because of the historical suggestion,



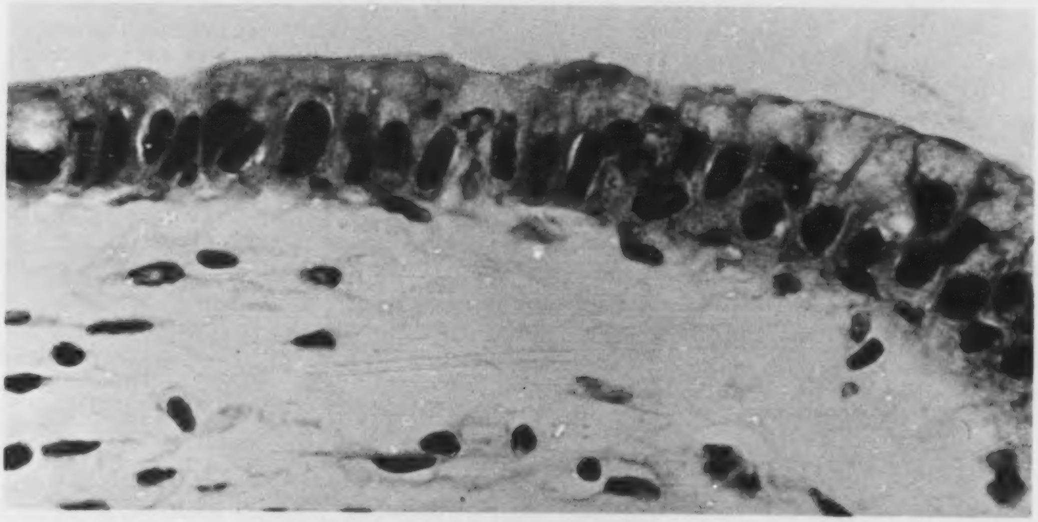


Figure 30B
SEVERE DYSPLASIA
(Top) Severe dysplastic epithelium overlying a group of antral type glands, two of which appear dilated. X200. (Bottom) Hyperchromatism and nuclear enlargement are prominent. A few atypical goblet cells are also present. X450.

to low cuboidal. The nuclei are enlarged, hyperchromatic, and usually contain a fine granular dispersed chromatin with one or two small nucleoli (fig. 31). The shape of the nuclei varies from spherical to elongated. The cytoplasm is eosinophilic, granular or vacuolated, and stains with PAS and alcian blue. Atypical goblet cells are also found in many cases. Dysplastic cells are usually aligned in a single layer, although pseudostratification can occur. They commonly extend into epithelial invaginations, but rarely into true mucous glands (fig. 32). Mitotic figures are not common.

The histologic features of carcinoma in situ vary only in degree when compared to dysplasia. The nuclei are larger and contain a coarse granular chromatin, while the nucleoli are more prominent and usually increased in number (figs. 33, 34). Giant cells with large hyperchromatic nuclei may be observed in some in situ carcinomas, and, in contrast to dysplasia, pseudostratification and even multilayering occur (fig. 35). Mitotic figures are relatively common. We should emphasize that the histologic differences between slight or moderate dysplasia and carcinoma in situ are sufficiently defined that these lesions can be diagnosed in cytologic preparations (see page 126). As in other organs, however, the distinction between severe dysplasia and carcinoma in situ is often arbitrary and not always possible.

According to their growth pattern, two types of carcinoma in situ are recognized: papillary and nonpapillary, the latter being more common. The papillary type is characterized by fibrous stalks that are covered by neoplastic cells and project into the lumen for short distances (fig. 36). We believe that this lesion is the precursor of papillary carcinoma.

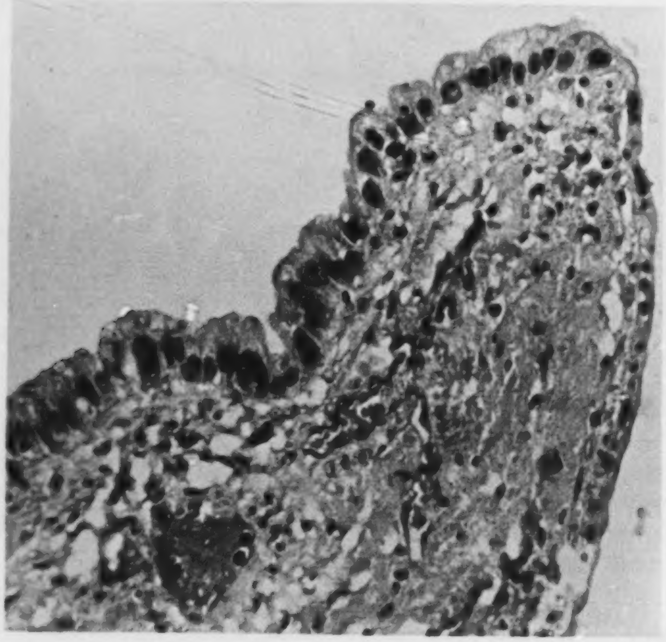


Figure 31
SEVERE DYSPLASIA
One side of this mucosal fold is lined by highly atypical epithelial cells having large hyperchromatic nuclei, some with prominent nucleoli. The opposite side is lined by atrophic epithelium. Cases like this one can be interpreted either as severe dysplasia or carcinoma in situ. X250.

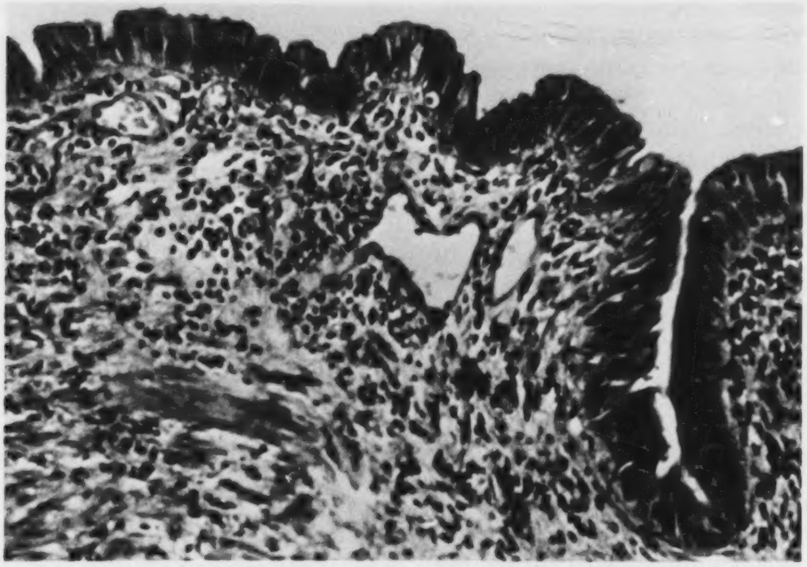


Figure 32
DYSPLASIA
Dysplastic cells, which have replaced the surface epithelium, have extended into an epithelial invagination. Inflammatory cells and dilated capillaries are present in the lamina propria. X250.

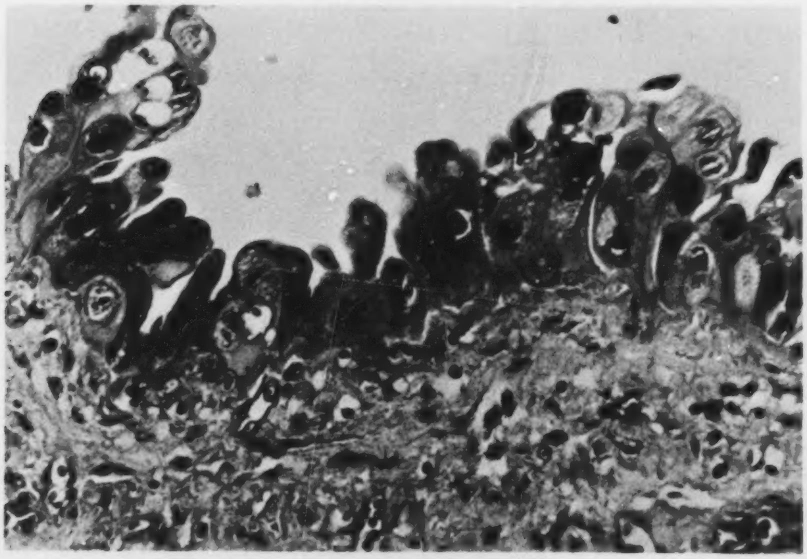


Figure 33
CARCINOMA IN SITU
The epithelial lining is neoplastic and highly atypical. Most cells have large bizarre hyperchromatic nuclei. The few cells that show vesicular nuclei contain prominent nucleoli. X350.

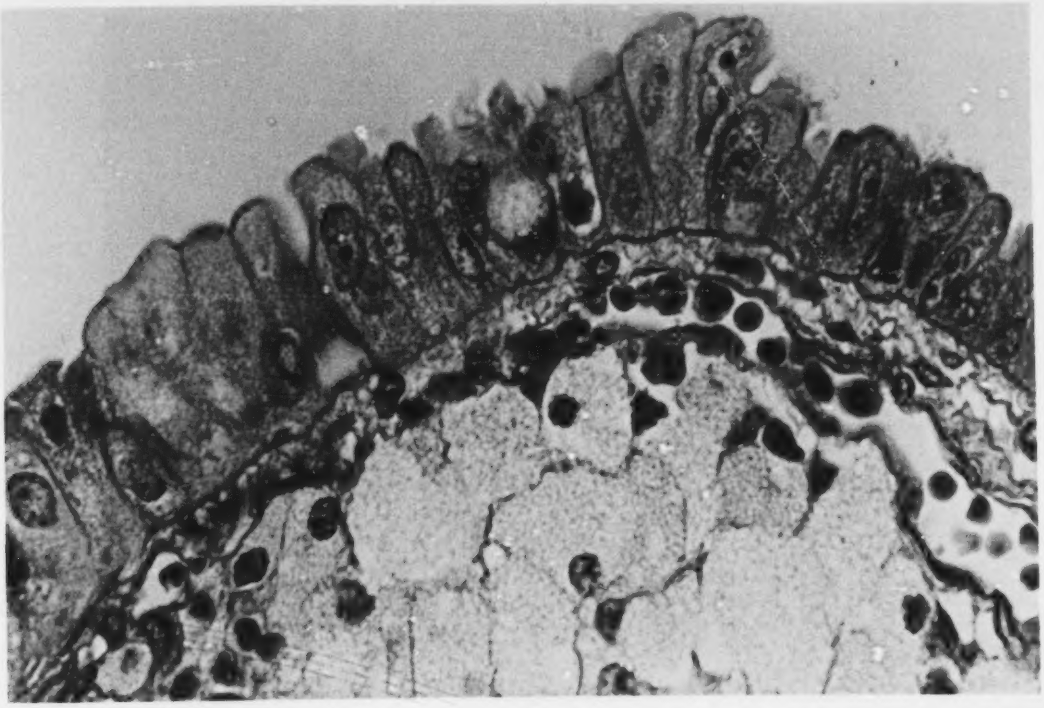


Figure 34
CARCINOMA IN SITU
The cells have enlarged and vesicular nuclei contain abnormal nucleoli. The basement membrane is clearly seen. Foam cells are present in the lamina propria. X700.

Carcinoma in situ may grow along the Rokitansky-Aschoff sinuses and even extend into the mucous glands located in the lamina propria. This extension should not be mistaken for stromal invasion (fig. 37).

Histologically, the evidence indicates progression from dysplasia to carcinoma in situ. For example, dysplasia is commonly found in the vicinity of carcinoma in situ. In fact, the two lesions are often continuous. In one of our cases of carcinoma in situ, subserial sections revealed microinvasive carcinoma arising from one of the in situ lesions. Moreover, dysplasia and carcinoma in situ are frequently seen adjacent to invasive carcinoma (fig. 38A). In one study, the remaining nonmalignant mucosa was abnormal in over 90 percent of cases of gallbladder carcinoma (Black et al.). These observations have led us to conclude that carcinomas of the gallbladder, as carcinomas in some other sites, originate from a field change within the epithelium.

In addition to the structural abnormalities, functional changes also occur in dysplasia and carcinoma in situ. Atypical goblet cells produce an abnormal mucin similar to the mucin elaborated by invasive carcinoma cells (Laitio, 1980). Moreover, cells from these two lesions contain CEA (pl. I-A), which is also present in invasive tumors,

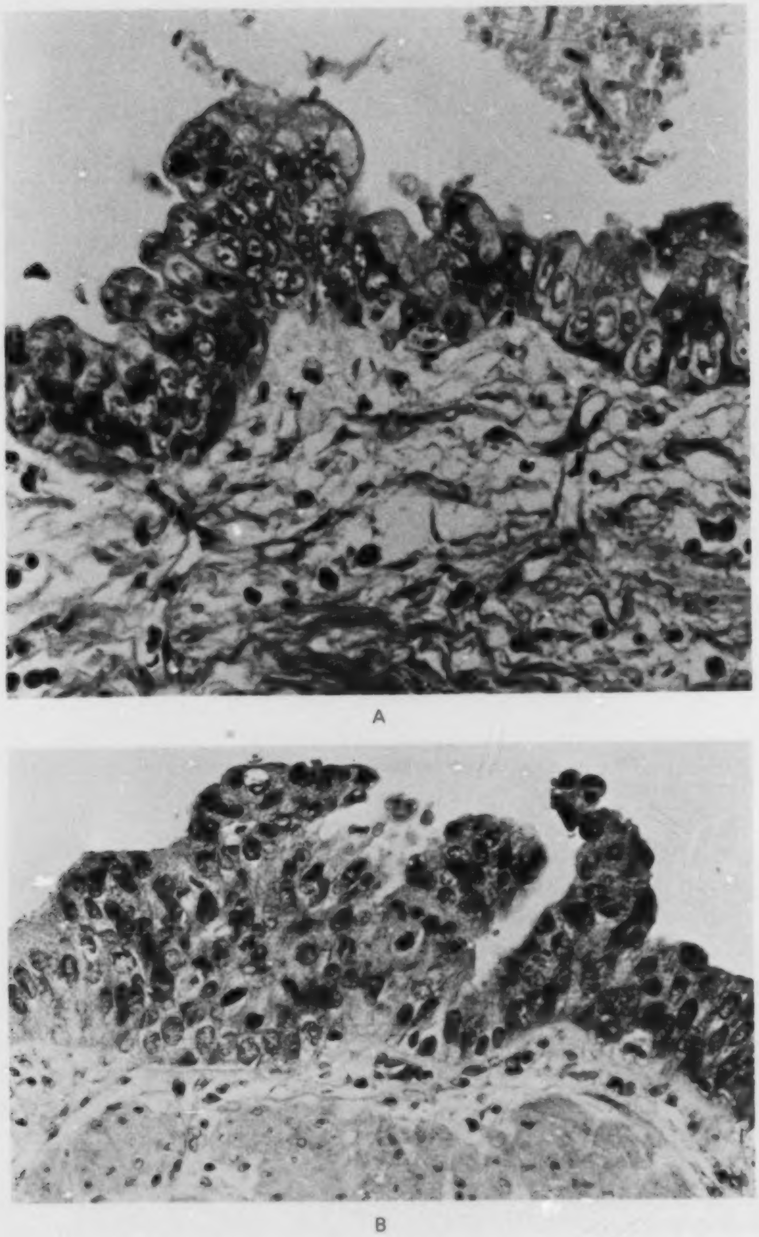


Figure 35
CARCINOMA IN SITU

(A) Pseudostratification and piling up of neoplastic cells is seen in an area of carcinoma in situ. Most cells contain prominent nucleoli. X300. (B) This carcinoma in situ shows several mitotic figures. X330.

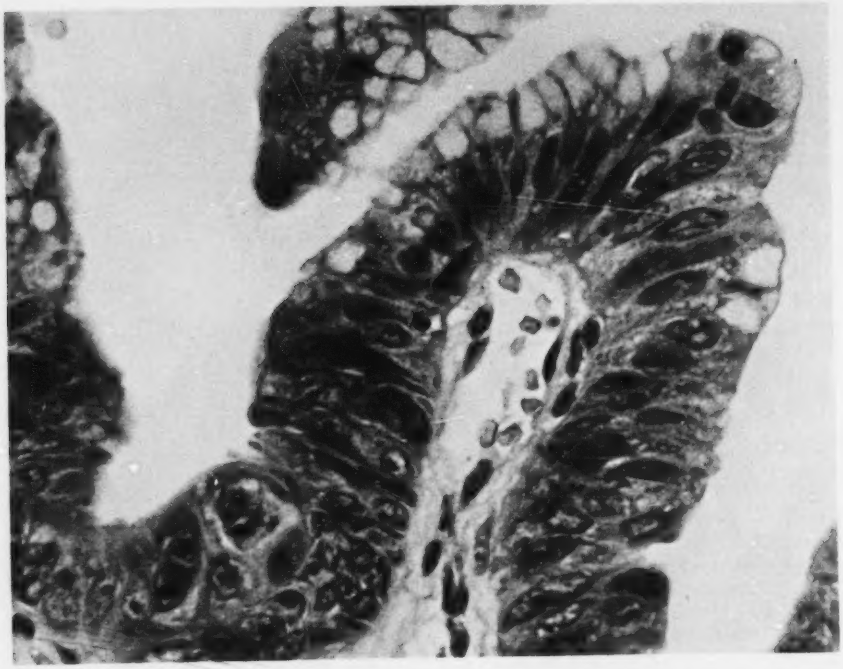


Figure 36
PAPILLARY CARCINOMA IN SITU
A small papillary projection is covered by neoplastic cells having prominent nucleoli. X450.

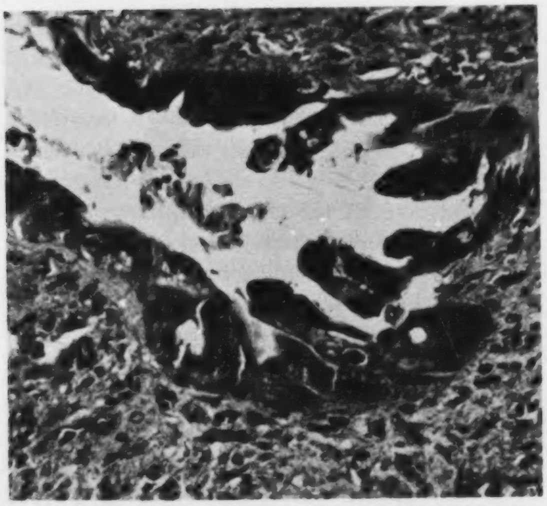


Figure 37
EXTENSION ALONG
ROKITANSKY-ASCHOFF SINUS
Neoplastic cells have extended along a Rokitansky-Aschoff sinus. This extension should not be mistaken for invasion. X250.

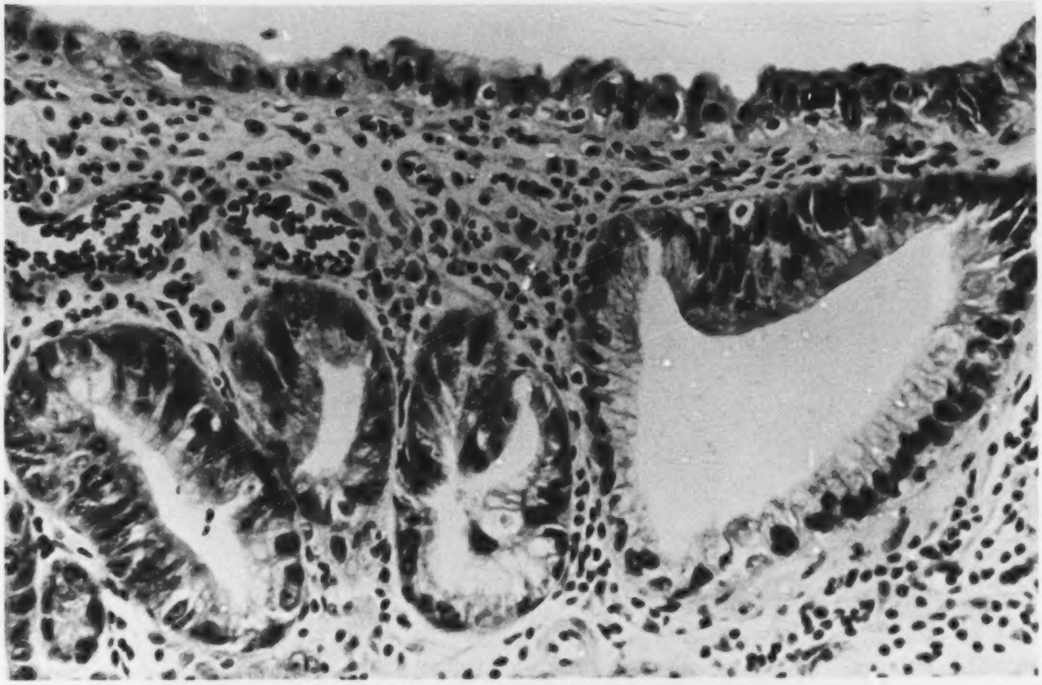


Figure 38A
INVASIVE CARCINOMA AND DYSPLASIA
An infiltrating adenocarcinoma is confined to the lamina propria. The overlying epithelium shows severe dysplasia. The coexistence of dysplasia, carcinoma in situ, and invasive carcinoma is the rule. X300.

but only in small amounts in normal epithelium. Rarely, in-situ carcinomas contain numerous goblet cells, Paneth cells, and endocrine cells, and are, therefore, considered to be the preinvasive phase of the intestinal type of adenocarcinoma (fig. 38B; see p. 72).

The rate of progression of these precursor lesions is unknown. In our cases, there is a five-year difference between the mean ages of patients with dysplasia and those with carcinoma in situ and a 10-year difference between the mean ages of patients with carcinoma in situ and those with invasive carcinoma.

It has also been reported that invasive carcinomas, especially papillary carcinomas, can arise in tubular or papillary adenomas (Kozuka et al.). Although this may occur in some cases, we believe that many, if not most, of these adenomas, which allegedly give rise to malignant tumors, are papillary carcinomas to begin with. In this regard, well differentiated adenocarcinomas, including papillary types, can show a spectrum of cytologic abnormalities that vary from minimal nuclear atypia to overt malignant changes. If a small papillary carcinoma consists predominantly of cells with minimal changes, then it may erroneously be considered as a benign lesion. Furthermore, the better differentiated areas

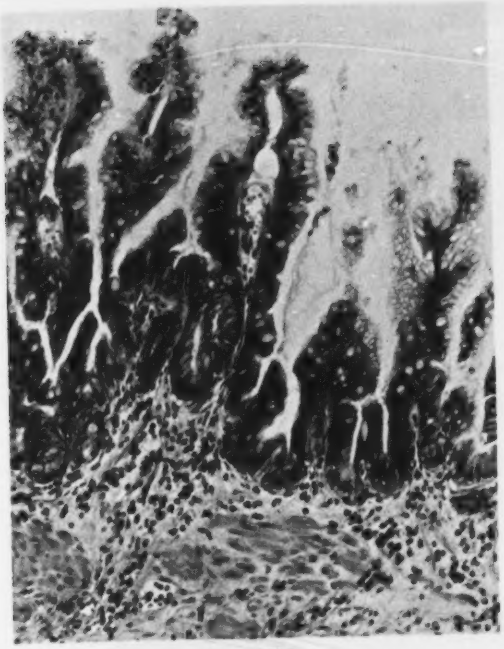


Figure 38B
INTESTINAL TYPE
CARCINOMA IN SITU

This papillary in situ carcinoma is composed of columnar cells, goblet cells and Paneth cells, the latter of which are difficult to recognize at this low power. Endocrine cells were also demonstrated with silver stains. X130.

of some tumors may be interpreted as the remnants of an adenoma. Also, hyperplasia of antral type glands, which often coexists with carcinoma, may be regarded as the residual of a tubular adenoma.

Other lesions which may predispose to carcinoma, such as squamous metaplasia, are discussed under "Tumor-like Lesions."

Atypical epithelial changes are often seen in cases of acute and chronic cholecystitis, especially when accompanied by mucosal ulceration and regeneration. These regenerating epithelial cells show prominent nucleoli, basophilic cytoplasm and even mitotic figures. In contrast to the cells seen in dysplasia and carcinoma in situ, however, these atypical cells are usually found along with cuboidal atrophic appearing cells, mucous secreting cells, and pencil-like cells. In short, dysplasia and carcinoma in situ have a monotonous appearing cell popoulation, whereas the atypia of repair has a heterogeneous population.

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GROSS FEATURES

Small infiltrating carcinomas may appear as a focal thickening of the gallbladder wall, a raised mucosal plaque, a bulging submucosal nodule, a polypoid structure protruding into the lumen, or a combination of these features. At an early stage, a small tumor may be confused with chronic cholecystitis and not recognized grossly (fig. 39). As carcinomas enlarge, some may cause diffuse thickening and induration of the entire gallbladder wall (fig. 40). Most carcinomas, however, grow as an infiltrating

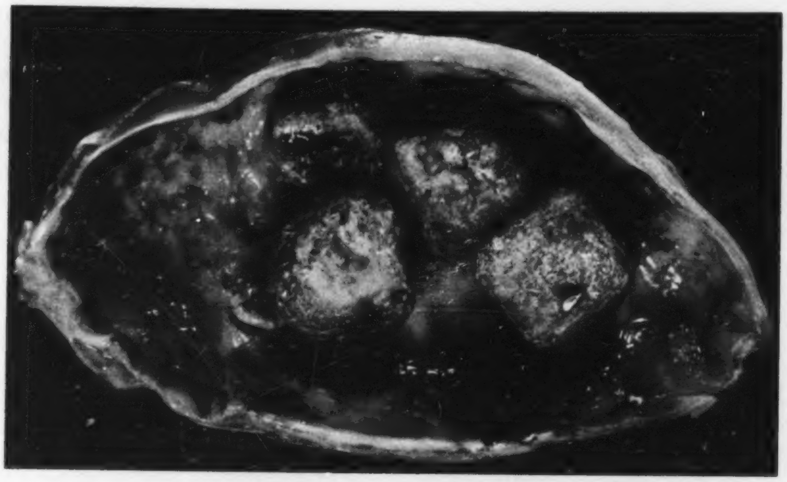


Figure 39
ADENOCARCINOMA
Gallbladder excised for cholelithiasis. A small infiltrating carcinoma, not grossly visible, was found in a thickened area of the wall. These early gross changes are difficult to recognize and are usually mistaken for chronic cholecystitis.

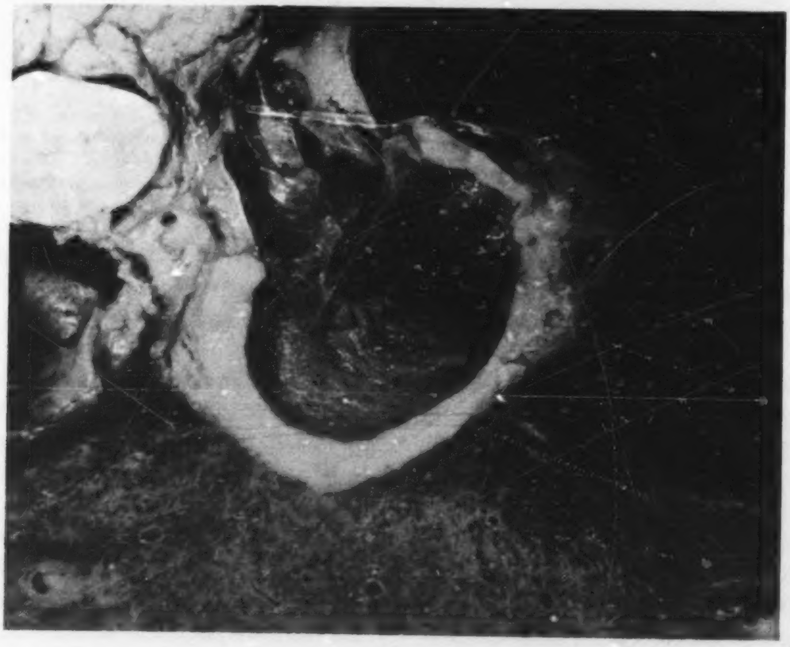


Figure 40
INTRAMURAL INFILTRATION
Diffuse intramural infiltration of a well differentiated adenocarcinoma that had also metastasized to a peripancreatic lymph node. In cases of diffuse infiltration, the site of origin of the tumor is not possible to specify.

gray white mass that can be recognized without much difficulty as a malignant neoplasm, and their site of origin can be located with some degree of certainty (fig. 41). The gallbladder may be distended by the tumor, contracted, or collapsed due to obstruction of the neck or cystic duct. It can also assume an hourglass deformity when the tumor arises in the body and causes constriction of the lateral walls.

Papillary carcinomas are usually sessile and exhibit a polypoid or cauliflower-like appearance (fig. 42; pl. I-B). Colloid and signet ring cell carcinomas have a mucoid or gelatinous cut surface. Although any type of gallbladder cancer may show necrosis, giant cell and oat cell carcinomas are usually the most necrotic (pl. I-C, D). Submucosal growth is an important feature of signet ring and oat cell carcinomas.

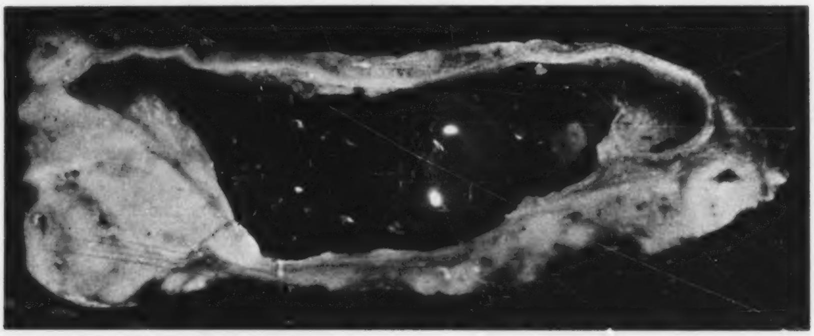


Figure 41
ADENOCARCINOMA
The usual gross features of a well differentiated adenocarcinoma are illustrated in this photograph. The tumor arose in the fundus and has extended subserosally to the body and neck.

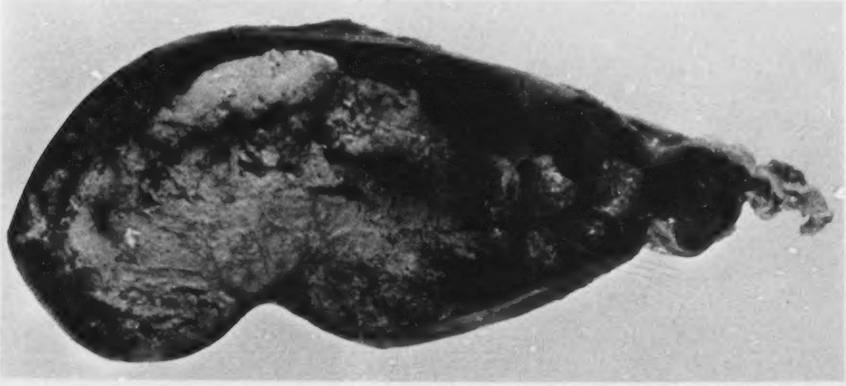


Figure 42
PAPILLARY ADENOCARCINOMA
A large papillary adenocarcinoma has filled most of the lumen of the gallbladder. Despite its large size, only a single focus of invasion was found. The dilatation at the origin of the cystic duct is Hartmann's pouch.

PLATE I

A. CARCINOMA IN SITU

Neoplastic cells contain CEA in the cytoplasm and along cell membranes. PAP CEA antibody. X200.

B. PAPILLARY ADENOCARCINOMA

This papillary adenocarcinoma arose from the body of the gallbladder. It has a cauliflower-like appearance and protrudes into the lumen. Despite its large size, limited invasion of the wall was demonstrated.

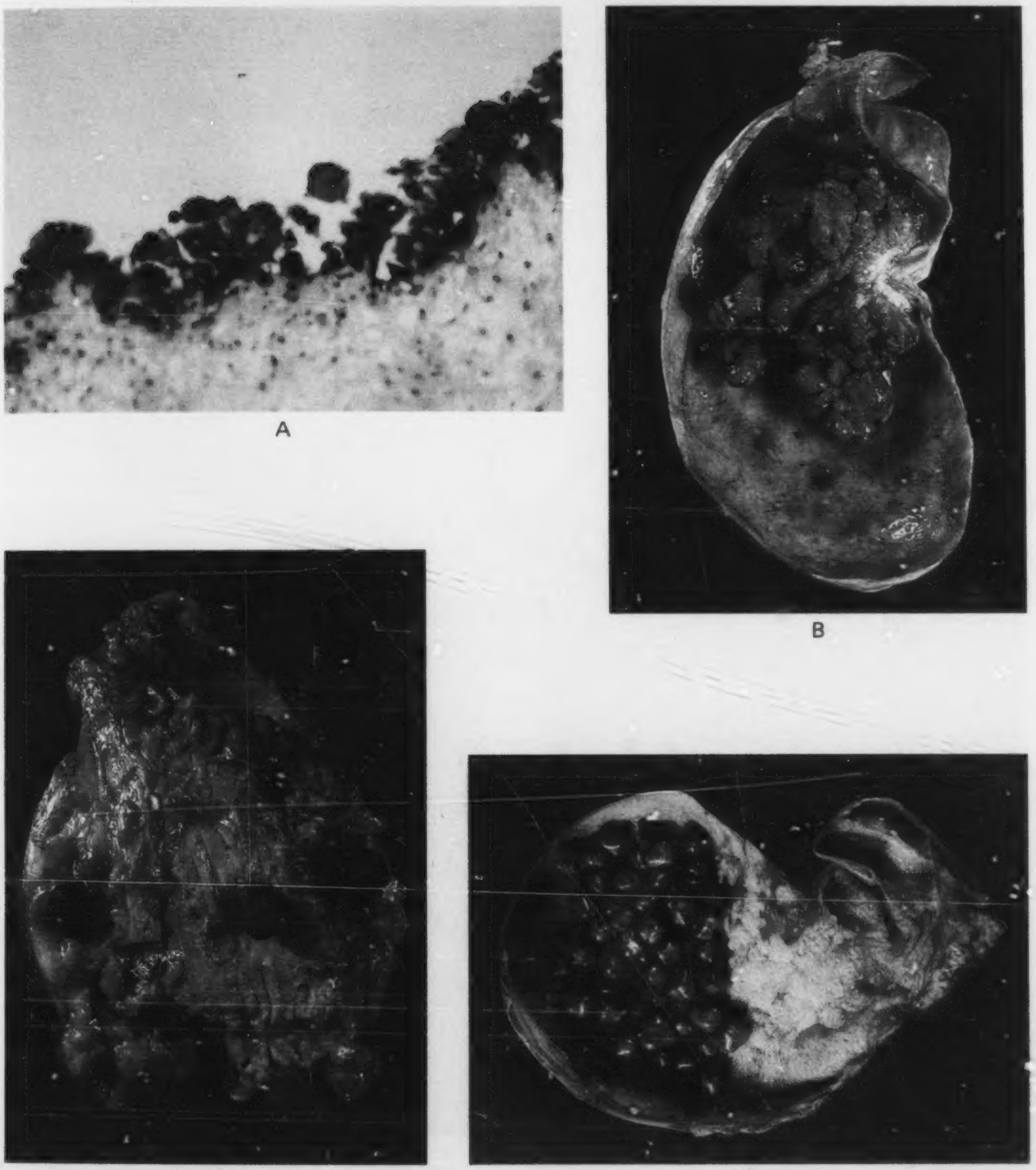
C. PLEOMORPHIC GIANT CELL ADENOCARCINOMA

The tumor, which is largely necrotic and associated with stones, has filled most of the lumen of the gallbladder.

D. OAT CELL CARCINOMA

This oat cell carcinoma, which arose in the body, shows extensive necrosis. It is associated with many stones.

PLATE I


A

B

C

D

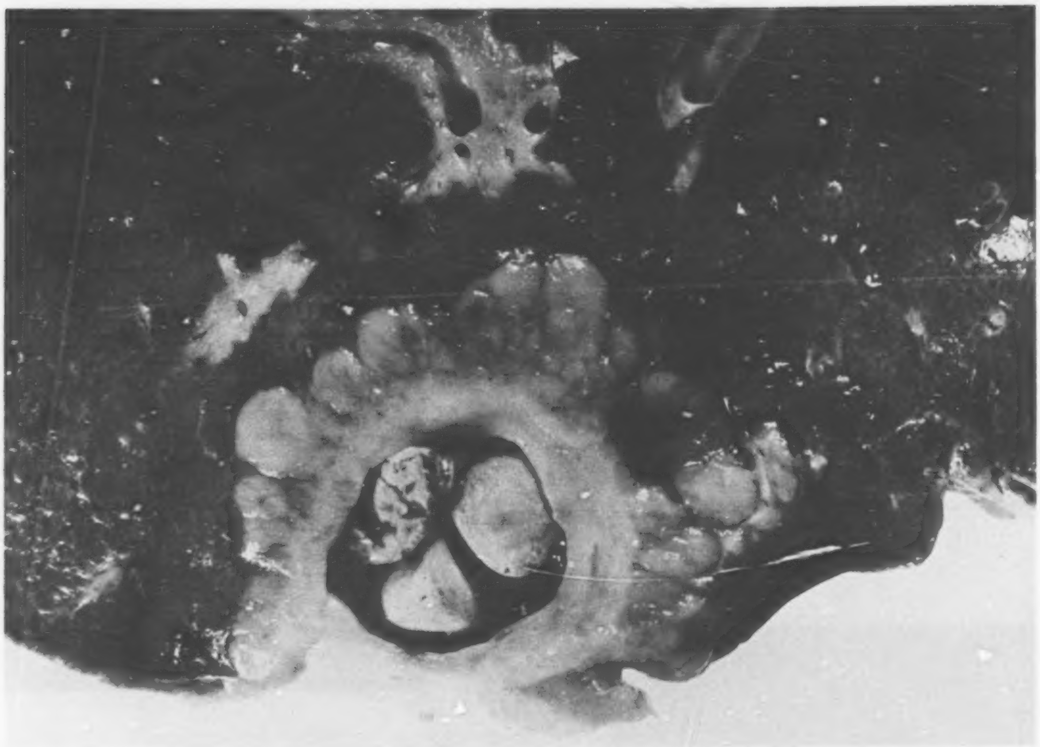


Figure 43
A NEOPLASTIC WALL
A thick neoplastic wall encases the gallbladder, which contains several stones. Histologically, this tumor was a signet ring cell carcinoma.

Gallbladder carcinomas arising in the neck not only lead to obstruction, which may result in hydrops, but commonly infiltrate the wall of the bile ducts including the mucosa, so that in some cases it is not possible to specify whether the tumor originated in the neck or in the cystic duct.

When extension to the liver takes place, the tumor often surrounds the gallbladder. The result is a thick neoplastic wall in which the gallbladder becomes encased (fig. 43).

Approximately 60 percent of carcinomas originate in the fundus, 30 percent in the body, and 10 percent in the neck. In some cases, the tumor may involve the entire gallbladder, apparently from diffuse intramural infiltration, and its origin is impossible to ascertain. Carcinoma can develop in a gallbladder stump years after a partial cholecystectomy (Arner and Von Schreeb; Cowley and Wood; Tanga et al.; see also p. 176).

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MICROSCOPIC DESCRIPTION

The histologic diagnosis of gallbladder cancer is usually not difficult for the pathologist. Nearly all cases involve some type of carcinoma which can be classified into one of the histologic categories (Table 1). None of these types is unique to the gallbladder. Most tumors exhibit more than one histologic pattern, any one of which may predominate.

Well Differentiated Adenocarcinoma

Well differentiated adenocarcinoma, the most common type, is characterized by a proliferation of different size glands which tend to branch and divide (fig. 44). Small tubular glands, medium size, glands, and large or cystically dilated glands may all be present in the same tumor (figs. 45–47). The glandular epithelium is characteristically tall columnar, less frequently cuboidal or, rarely, flat and then superficially resembles endothelium (fig. 48). The round, oval, or elongated basal or centrally located nuclei are often vesicular with marginal chromatin, although coarsely granular diffusely distributed chromatin often results in nuclear hyperchromatism (figs. 49, 50). The cytoplasm is eosinophilic or slightly granular, but can also be pale or clear. Goblet cells located between the columnar or cuboidal cells are occasionally present.

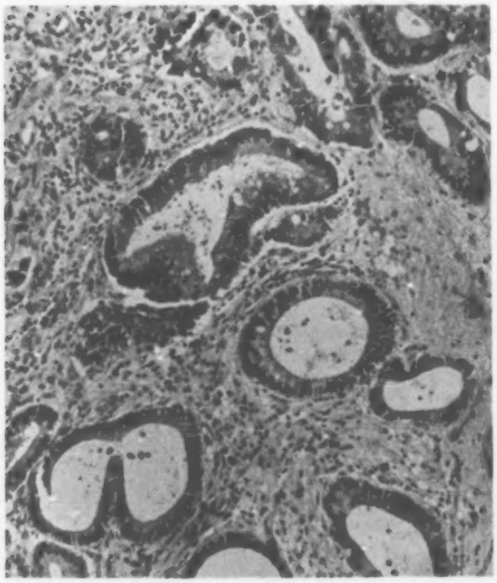


Figure 44
WELL DIFFERENTIATED ADENOCARCINOMA
A well differentiated adenocarcinoma is composed of variable shaped glands lined by neoplastic columnar cells and separated by a fibrous stroma. X175.

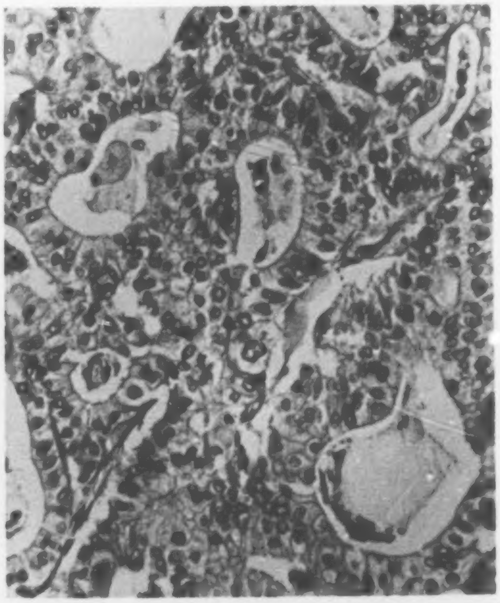


Figure 45
WELL DIFFERENTIATED ADENOCARCINOMA
Well differentiated adenocarcinoma showing closely packed glands with very little intervening stroma. X180.

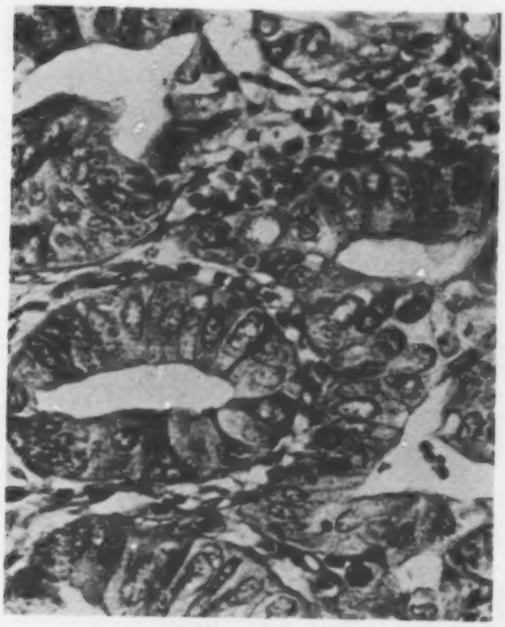


Figure 46
WELL DIFFERENTIATED ADENOCARCINOMA
Well differentiated adenocarcinoma made up of small but rather uniform glands lined by columnar cells. X300.

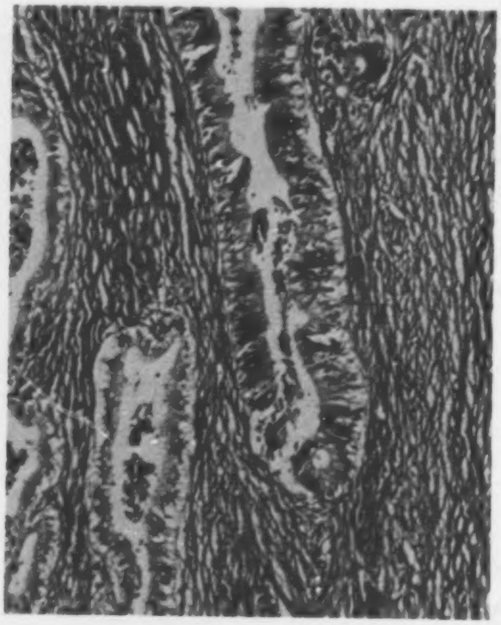


Figure 47
WELL DIFFERENTIATED ADENOCARCINOMA
In contrast to the tumor shown in figure 46, this adenocarcinoma is composed of long tubular glands supported by an abundant fibrous stroma. X180.

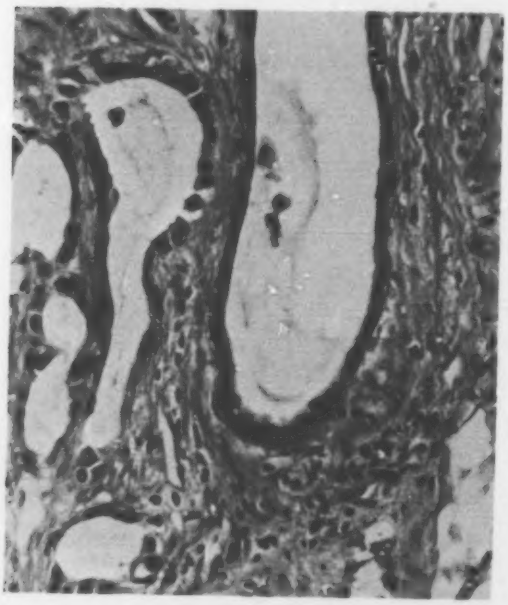


Figure 48
WELL DIFFERENTIATED ADENOCARCINOMA
This well differentiated adenocarcinoma contains glands lined by low cuboidal or flat epithelium similar to the atrophic epithelium seen in chronic cholecystitis. X200.

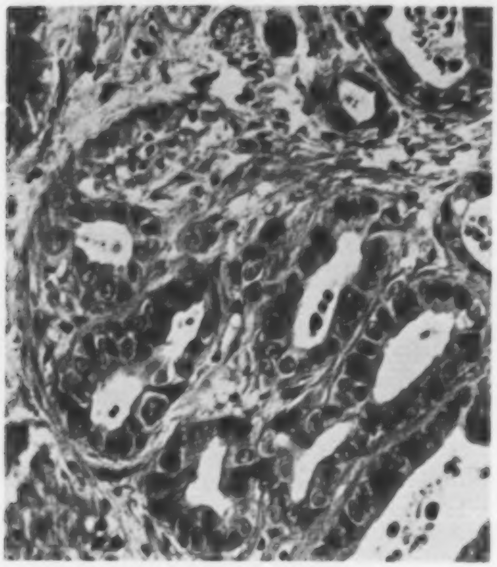


Figure 49
WELL DIFFERENTIATED ADENOCARCINOMA
In this well differentiated adenocarcinoma, the neoplastic cells show greater nuclear pleomorphism and the nucleoli are more prominent. These changes are within the limits of a well differentiated adenocarcinoma. X200.

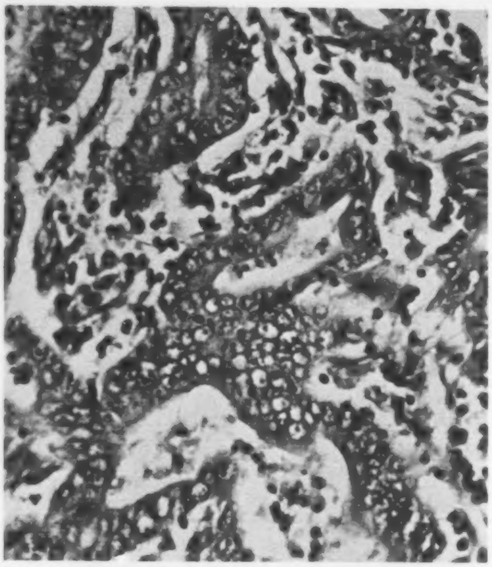


Figure 50
WELL DIFFERENTIATED ADENOCARCINOMA
The nuclei of this well differentiated adenocarcinoma have a vesicular appearance. Vesiculation of nuclei is occasionally seen in carcinoma of the gallbladder. X275.

The number of mitotic figures varies considerably; in some tumors they are numerous, while in others they are relatively rare. In some tumors, the neoplastic cells show focal growth as sheets, cords, or even rows, in addition to forming glands.

With the PAS, alcian blue and colloidal iron stains, mucin can be detected in some cells and in the lumen of the neoplastic glands (pl. II-A, B). The amount of intra- and extracellular mucin, however, is variable even in different areas of the same tumor. This substance is predominantly a nonsulfated acid and neutral mucin (Laitio and Terho). Occasionally, the PAS and alcian blue stain only the apical border or luminal surface of the cell. The diagnosis of well differentiated adenocarcinoma should depend on the formation of glands and not on the mucin content.

The wall of the gallbladder shows variable degrees of fibrosis as well as an acute or chronic inflammatory cell infiltrate that may also be present within the lumen of the neoplastic glands (fig. 51). The fibrous tissue may widely separate these glands, especially in tumors with excessive desmoplasia. Even though these tumors are often described as scirrhous, they still belong to the well differentiated category. Occasionally, carcinomatous glands, particularly in the early stages, will invade the lamina propria and muscle layer without provoking a fibroblastic reaction (fig. 52). Neoplastic growth along Rokitansky-Aschoff sinuses is also seen (fig. 53).

With the immunoperoxidase technic, CEA can be detected in the epithelial cells and in gland secretions.

PLATE II

A. WELL DIFFERENTIATED ADENOCARCINOMA

Intracellular and extracellular PAS positive material is seen. X200.

B. WELL DIFFERENTIATED ADENOCARCINOMA

Alcian blue positive material is present, predominantly in the gland lumen. X200.

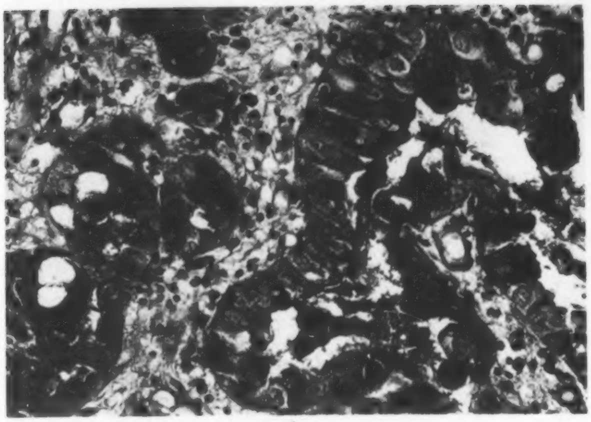
C. PAPILLARY ADENOCARCINOMA

Neoplastic glands contain CEA along the apical cell membrane and within the cytoplasm. PAP CEA antibody. X150.

D. ATYPICAL CARCINOID

A small umbilicated submucosal nodule is present in the body of the gallbladder.

PLATE II



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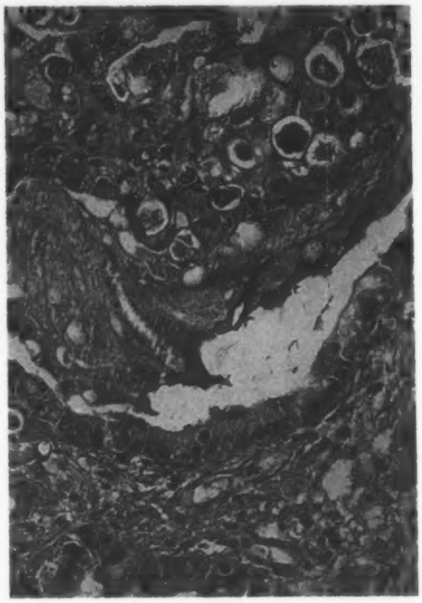

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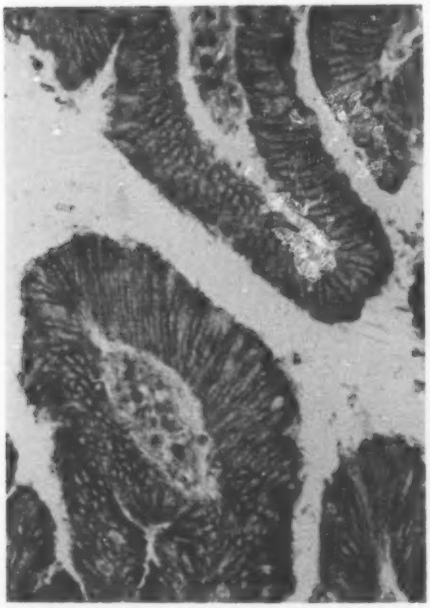

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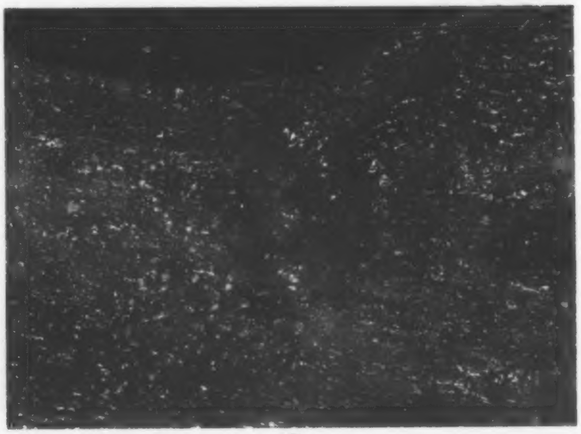

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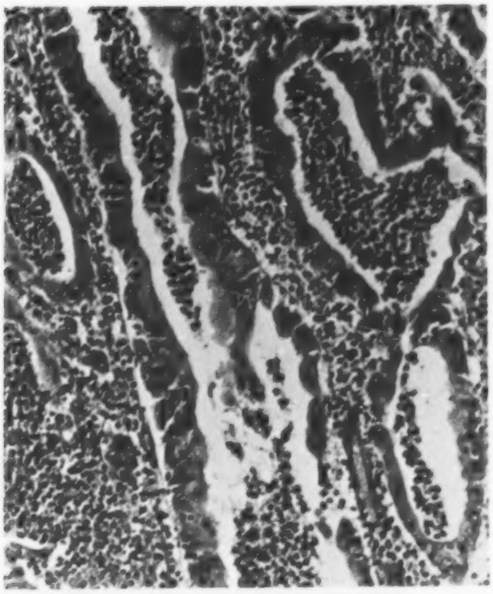

Figure 51
WELL DIFFERENTIATED ADENOCARCINOMA
The glands of this well differentiated adenocarcinoma are filled with polymorphonuclear leukocytes. This extensive inflammatory cell infiltration is not common in well differentiated adenocarcinomas. X140.

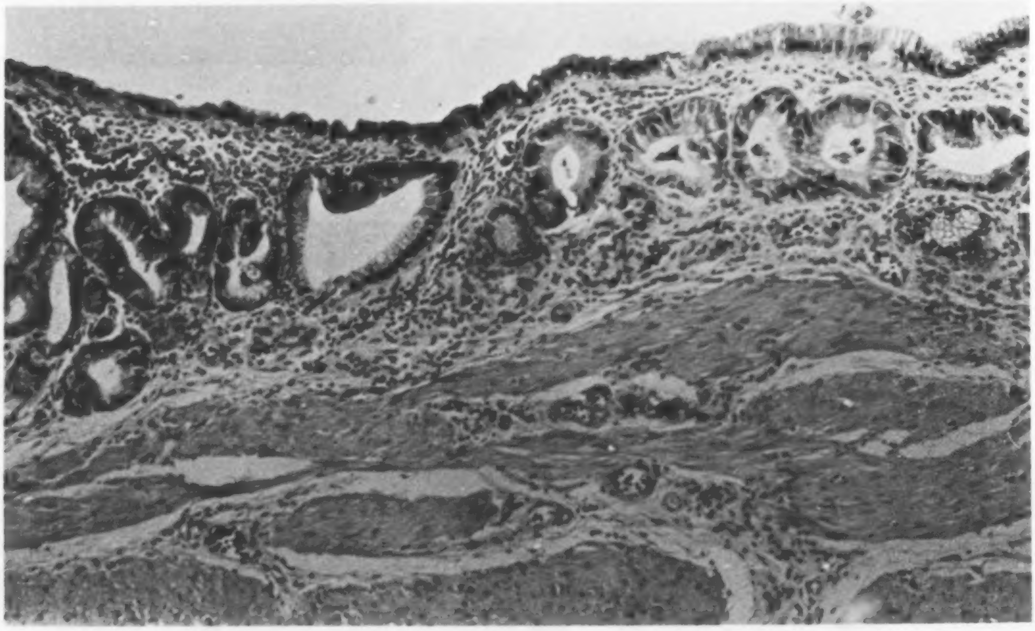

Figure 52
WELL DIFFERENTIATED ADENOCARCINOMA
A well differentiated adenocarcinoma has extended along the lamina propria without provoking a desmoplastic reaction. In other areas, the tumor invaded the muscle layer. In areas such as this, it is difficult to determine invasion. X100.

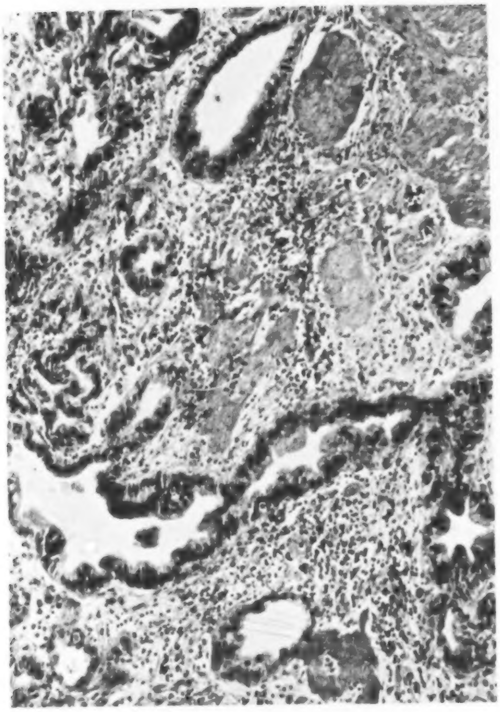

Figure 53
WELL DIFFERENTIATED ADENOCARCINOMA
An infiltrating well differentiated adenocarcinoma has extended along a Rokitansky-Aschoff sinus. X100.

Papillary Adenocarcinoma

Papillary carcinoma is a well differentiated adenocarcinoma that grows outward from the epithelial surface (fig. 54). The tumor consists of branching fibrovascular stalks of different width and length, lined by cuboidal or columnar cells with basal hyperchromatic nuclei and a vacuolated cytoplasm containing mucin (fig. 55; pl. II-C). Foci of intestinal metaplasia, consisting of goblet cells, argyrophil and argentaffin cells, as well as a few Paneth cells, are present in some tumors. The nuclear atypia and number of mitotic figures vary considerably in different tumors. Cases with slight atypia, few mitoses, and minimal invasion are often difficult to distinguish from papillary adenomas.

These papillary carcinomas may fill the lumen of the gallbladder before invading the wall (fig. 56). For this reason, they are associated with a better prognosis than tumors that infiltrate early. In general, the infiltrating portion of the tumor forms well differentiated glands rather than papillary structures, but in some areas the papillary pattern is preserved, even in metastatic deposits (fig. 57). Some papillary carcinomas are associated with anaplastic small cells or squamous foci, especially in the deeper parts of the tumor.

Pleomorphic Giant Cell Adenocarcinoma

Pleomorphic giant cell adenocarcinomas exhibit a histological structure similar to those found in other organs, such as in the thyroid gland, pancreas, and lung. They are the most pleomorphic tumors of the group and are characterized by variable proportions of polygonal, round, spindle, and multinucleated giant cells showing no particular histologic differentiation (fig. 58). Characteristically, these cells have large bizarre nuclei and prominent nucleoli (fig. 59). Any one of the four cell types may predominate in different areas, but, in all cases, the spindle and giant cells are more common. Areas of a well differentiated adenocaricnoma are found in approximately two-thirds of these tumors (fig. 60), and areas that we interpret as transitions between well differentiated glands and pleomorphic elements in about one-third of the cases (fig. 61).

A small amount of mucin and CEA can usually be found in the glands and in the spindle and giant cells. Some of the giant

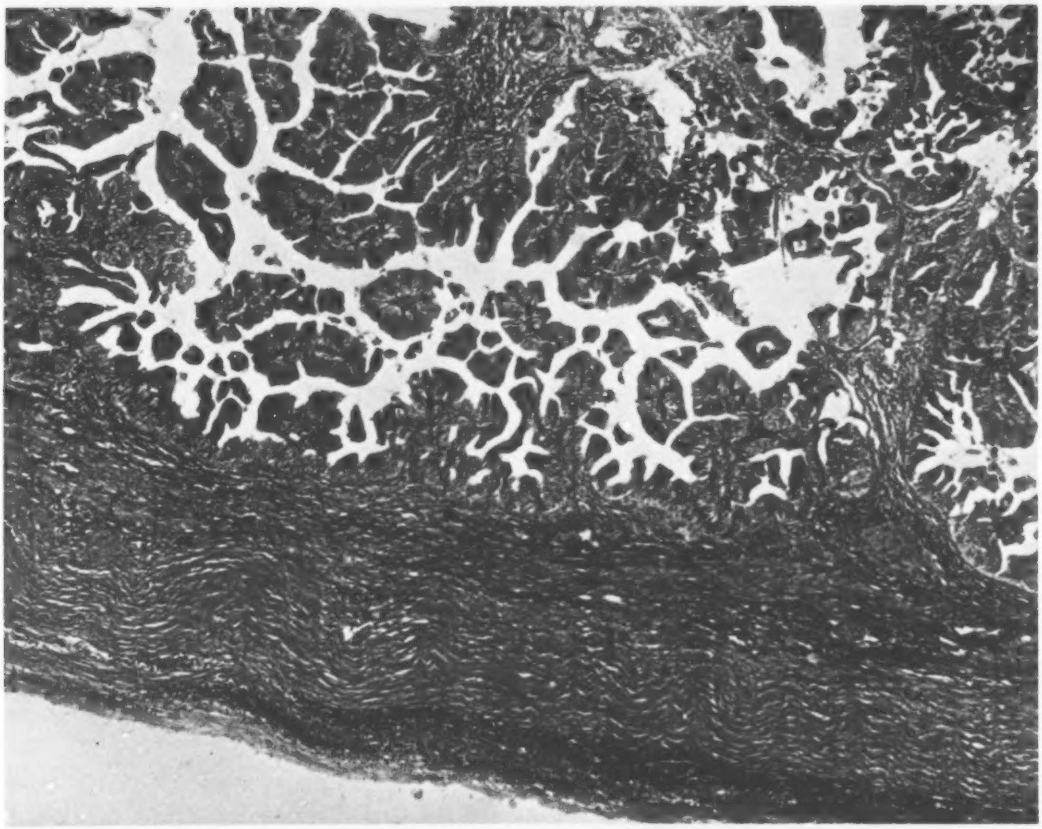

Figure 54
PAPILLARY ADENOCARCINOMA

A papillary adenocarcinoma is growing into the lumen of the gallbladder. In this section, the wall of the gallbladder, which is thickened and fibrotic, has not been invaded. X35.

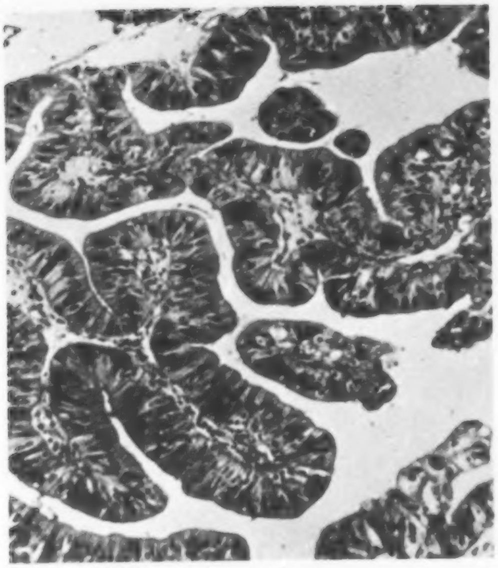

Figure 55
(Figures 55 and 56 from same patient)
PAPILLARY ADENOCARCINOMA

Infiltrating papillary carcinoma. The papillary structures are lined by tall uniform columnar cells that show little nuclear pleomorphism. X150.

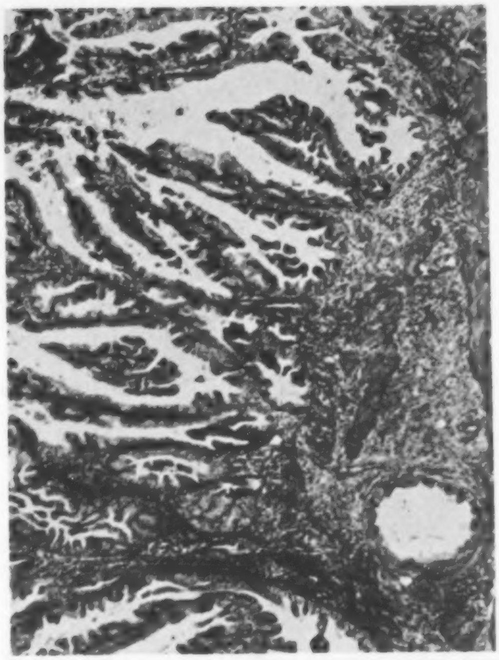

Figure 56
PAPILLARY ADENOCARCINOMA

This papillary adenocarcinoma shows invasion into the lamina propria and muscle coat. A neoplastic gland is visible in the wall of the gallbladder. X35.

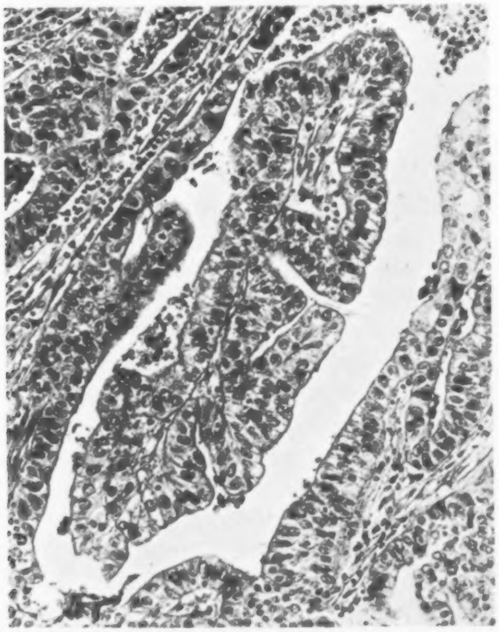

Figure 57
PAPILLARY ADENOCARCINOMA

An infiltrating papillary adenocarcinoma has retained its papillary growth pattern even within a neoplastic gland. These intraglandular papillary patterns can also be seen in metastatic lesions. X140.

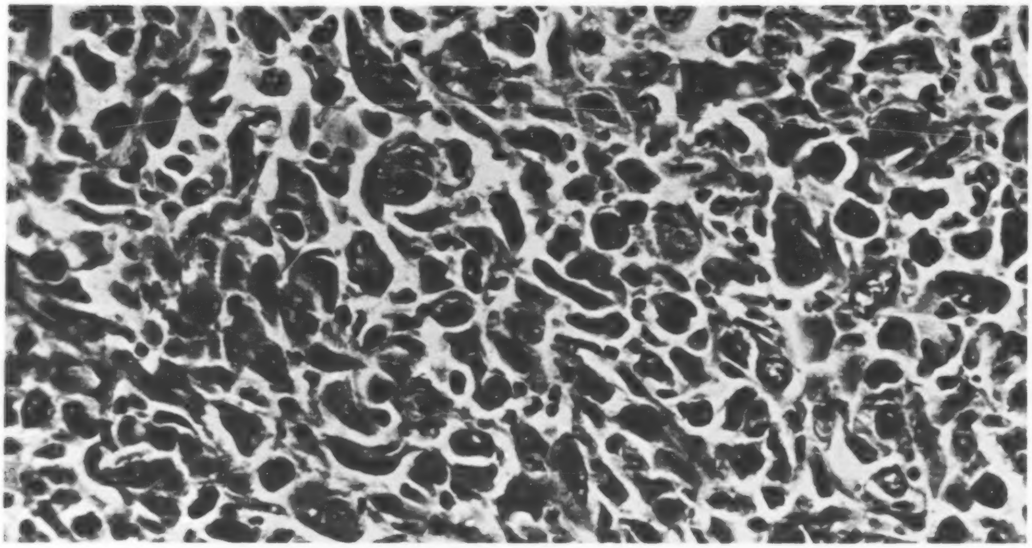

Figure 58
PLEOMORPHIC GIANT CELL ADENOCARCINOMA
A characteristic appearance of a pleomorphic giant cell adenocarcinoma of the gallbladder. X300.

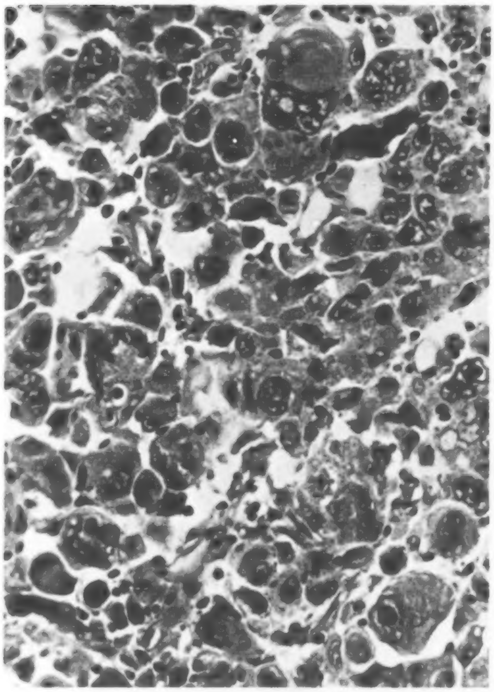

Figure 59
PLEOMORPHIC GIANT CELL ADENOCARCINOMA
Large bizarre cells like these often form the bulk of some pleomorphic giant cell adenocarcinomas. X300.

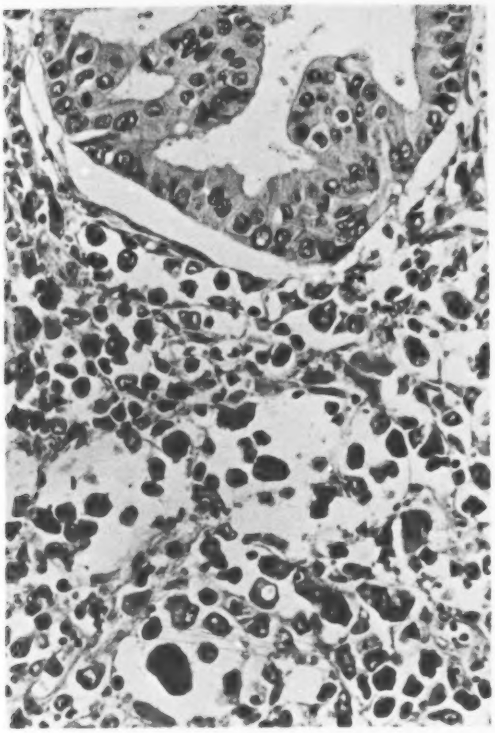

Figure 60
PLEOMORPHIC GIANT CELL ADENOCARCINOMA
A well differentiated neoplastic gland is present in a pleomorphic giant cell adenocarcinoma. X160.

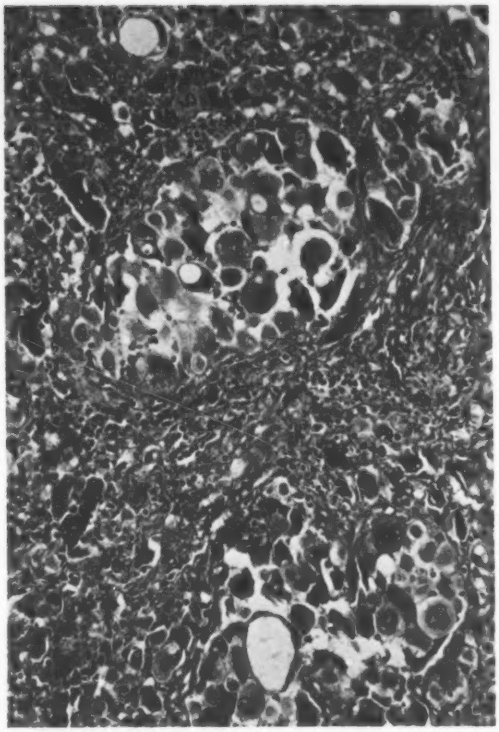

Figure 61
PLEOMORPHIC GIANT CELL ADENOCARCINOMA
Two poorly defined glands are partially filled with rather large pleomorphic epithelial cells. We have considered these areas as representing transitions from well differentiated to pleomorphic giant cell adenocarcinomas. X160.

cells may contain phagocytized red blood cells, polymorphonuclear leukocytes, lymphocytes, or nuclear debris in various stages of degeneration (fig. 62). The spindle cells can simulate mesenchymal cells and, in cases where they predominate, may lead to a mistaken diagnosis of sarcoma (fig. 63).

A few spindle and multinucleated giant cells contain distinct PAS positive hyaline globules (fig. 64) which are also present in an extracellular location, presumably the result of extrusion from the cells. They are found in about 10 percent of pleomorphic giant cell adenocarcinomas. In one of our cases, these globules stained positive for alpha-fetoprotein with immunocytochemical methods. Similar globules which contained alpha-1-antitrypsin were described in a well differentiated adenocarcinoma of the gallbladder occurring in a patient with partial alpha-1-antitrypsin deficiency (Callea et al.).

Areas of squamoid differentiation can be detected in 20 percent of these tumors. Because of foci of well differentiated glands, transitions from well differentiated glands to pleomorphic elements, and the presence of CEA and mucin in spindle and

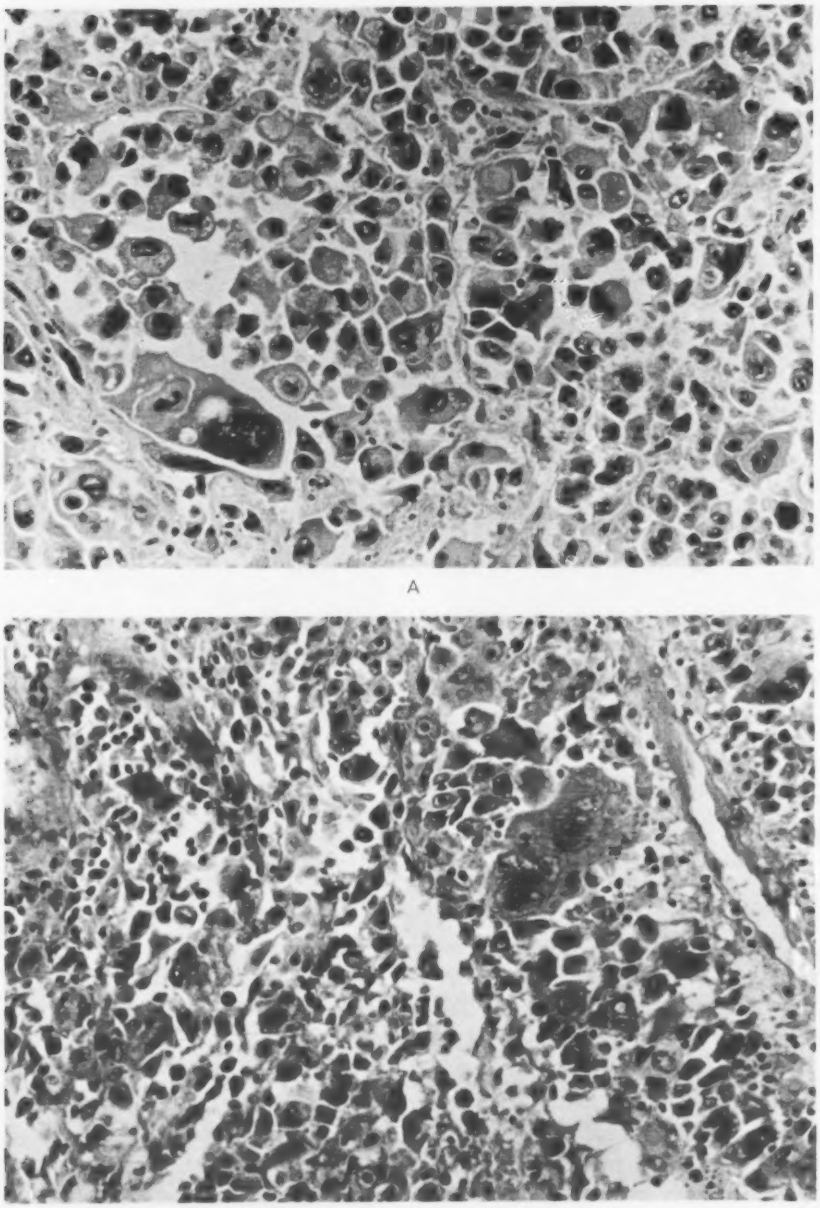

Figure 62
PLEOMORPHIC GIANT CELL ADENOCARCINOMA
(A and B) Large multinucleated giant cells contain phagocytized erythrocytes, polymorphonuclear leukocytes, and nuclear debris. This is a common feature in many pleomorphic giant cell adenocarcinomas. X180.

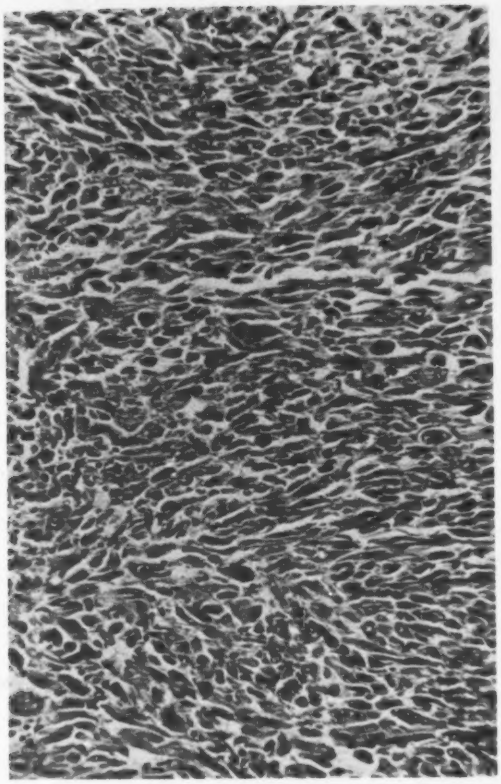

Figure 63
PLEOMORPHIC GIANT CELL ADENOCARCINOMA
This pleomorphic giant cell adenocarcinoma is composed predominantly of spindle cells. These areas can resemble a sarcoma. X150.

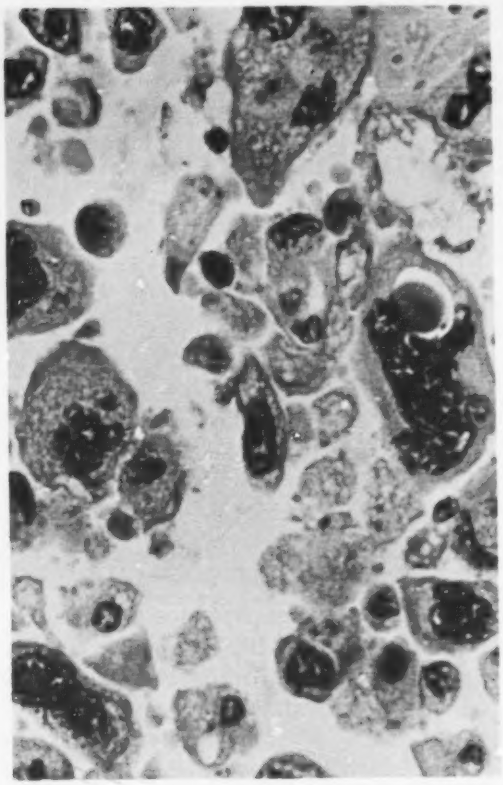

Figure 64
PLEOMORPHIC GIANT CELL ADENOCARCINOMA
A neoplastic giant cell contains a round hyaline globule surrounded by a clear halo. These globules, which are PAS positive, resemble those found in endodermal sinus tumors and in some hepatomas. X375.

giant cells, these pleomorphic tumors are classified as a type of adenocarcinoma.

An inflammatory infiltrate composed of lymphocytes and polymorphonuclear leukocytes is often seen in the stroma. Extensive necrosis is another common finding in these tumors.

One tumor in our series contained osteoclast-like multinucleated giant cells surrounded by polygonal and spindle cells, a pattern consistent with malignant giant cell tumor of the bone (fig. 65). We consider this tumor a variant of giant cell carcinoma, because in some areas the usual pattern of a giant cell adenocarcinoma was present, including glands. Similar osteoclastoma-like tumors have been reported in the thyroid, pancreas, and liver. Some investigators believe these tumors are epithelial in origin (Albores-Saavedra et al., 1972, 1981; Rosai).

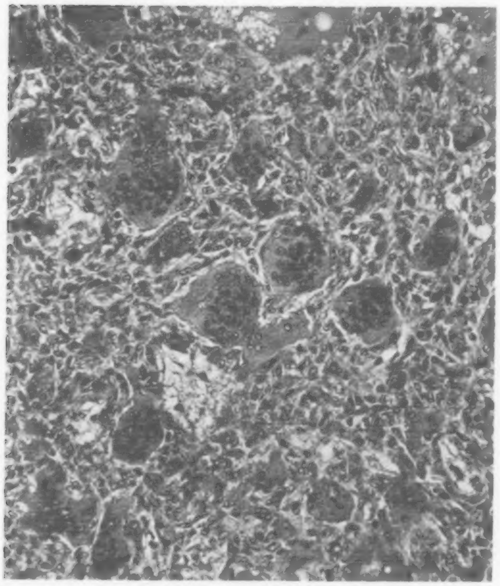

Figure 65
PLEOMORPHIC GIANT CELL ADENOCARCINOMA
An osteoclastoma-like pattern is present in a pleomorphic giant cell adenocarcinoma. X160.

Intestinal Type Adenocarcinoma

This type, we believe, is a variant of the well differentiated adenocarcinoma. However, because it resembles intestinal epithelium, it should be separated from the well differentiated group. One type is composed of different sized glands lined chiefly by goblet cells (fig. 66). These cells have basal hyperchromatic nuclei and a cytoplasm distended by single or multiple mucinous vacuoles (fig. 67). These distended cells seem to compress adjacent columnar cells, some of which contain no mucous material. A small number of argyrophil and argentaffin cells, identified with the Grimelius and Fontana Masson stain, respectively, are present in some of these tumors. Paneth cells are found in a smaller number. The glands contain variable amounts of mucous material.

A second type of intestinal adenocarcinoma consists of glandular structures that resemble those of colonic adenocarcinoma (figs. 63, 69). The epithelium usually has a well defined brush border, and most columnar cells contain mucus. Only a few goblet cells are interspersed between columnar cells. Very often, these tumors are mixed and show, in addition, the pattern of an ordinary well differentiated adenocarcinoma of the gallbladder. The number of mitotic figures varies from tumor to tumor, but generally they are not common.

The distinction between the two types of intestinal adenocarcinomas depends on the number of goblet cells, which are predominant in the first type. In addition, the first type contains little CEA, while this substance is abundant in the second type.

Intestinalization can occur as a focal change in other adenocarcinomas, especially the well differentiated, papillary, and poorly differentiated small cell types. However, isolated endocrine cells or Paneth cells are more often seen than the fully developed intestinal metaplasia which includes all cell types.

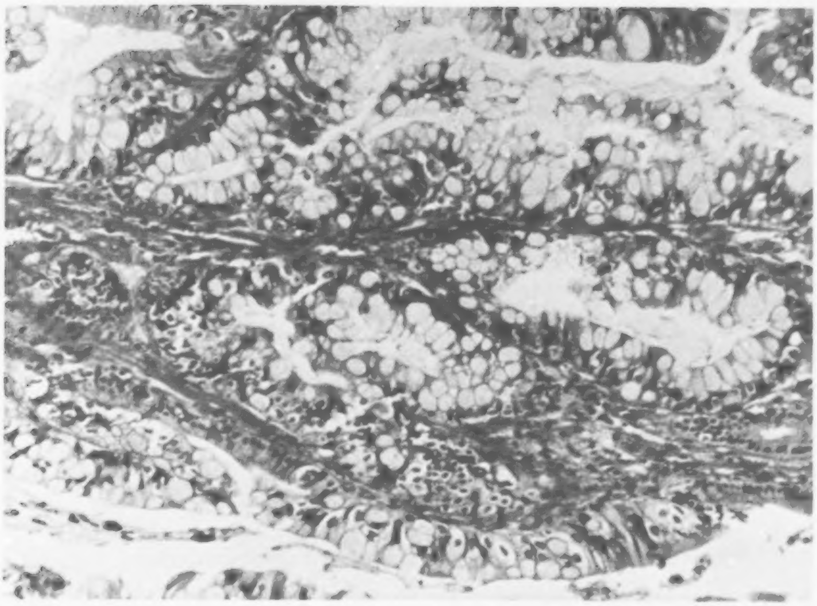

Figure 66
INTESTINAL TYPE ADENOCARCINOMA
The neoplastic glands of this intestinal type adenocarcinoma are lined almost exclusively by goblet cells. X140.

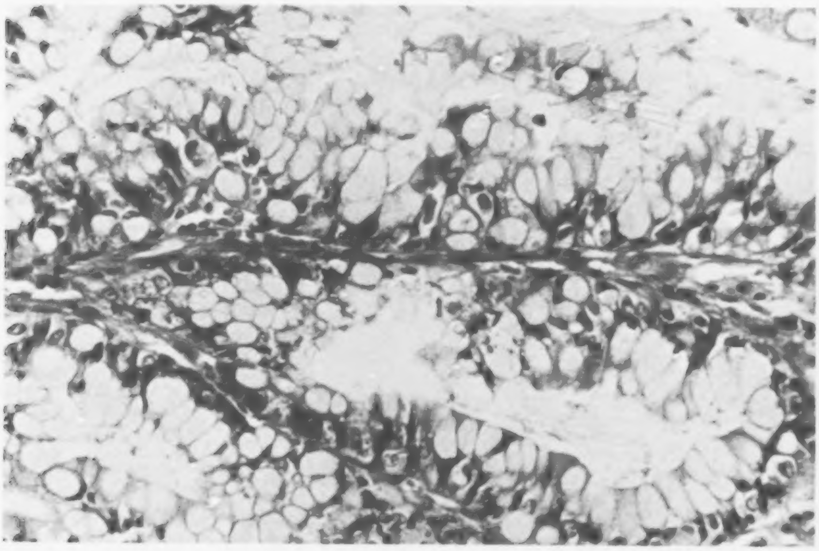

Figure 67
INTESTINAL TYPE ADENOCARCINOMA
A high magnification showing part of three glands lined with neoplastic, but well differentiated, goblet cells. X250.

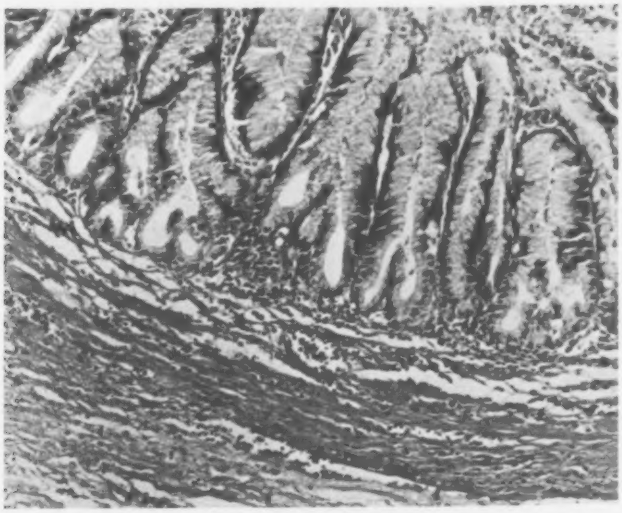

Figure 68
INTESTINAL TYPE ADENOCARCINOMA
Branching colonic-like tubular glands are lined by mucus-secreting columnar cells. X100.

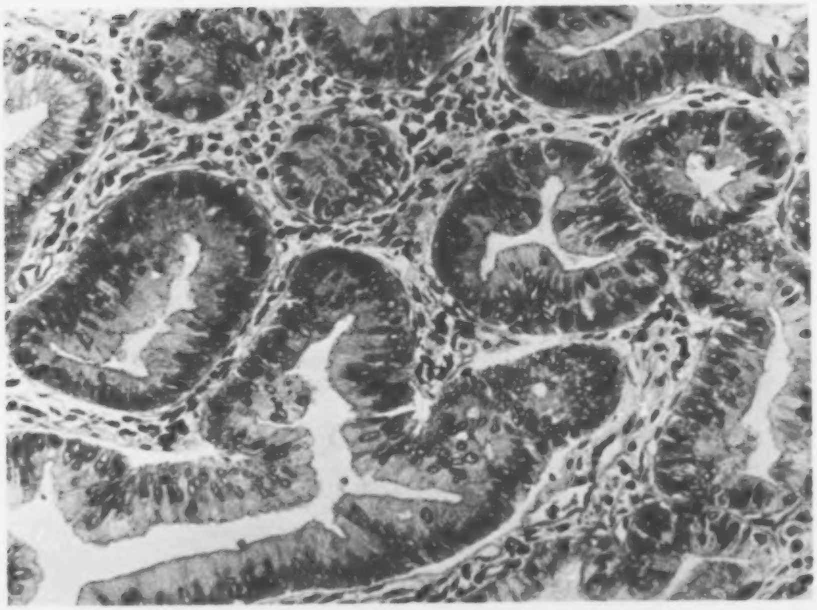

Figure 69
INTESTINAL TYPE ADENOCARCINOMA
Glandular structures are similar to those of a well differentiated colonic adenocarcinoma. The cytoplasm of most cells lacks mucin. X180.

Poorly Differentiated Adenocarcinoma, Small Cell Type

Described in the original Fascicle as undifferentiated small cell adenocarcinoma, this tumor is characterized by the proliferation of small round cells that grow in nodules, single rows, solid sheets, nests, cords, or trabeculae (figs. 70, 71). Individual cells which are not cohesive contain round or ovoid vesicular or hyperchromatic nuclei with prominent nucleoli (figs. 72, 73). The cytoplasm is eosinophilic or vacuolated. In some areas, large polygonal cells with pleomorphic nuclei and even giant cells are found. Rarely, a few signet ring cells are noted. The stroma usually shows variable fibrosis and contains chronic inflammatory cells. Mitotic figures are numerous. Vascular invasion is common. Extensive necrosis is another constant feature of these tumors.

Because there is some gland formation and mucin can be detected in many cells and in the gland lumina, we prefer the term "poorly differentiated adenocarcinoma, small cell type." Furthermore, CEA is present in some cells.

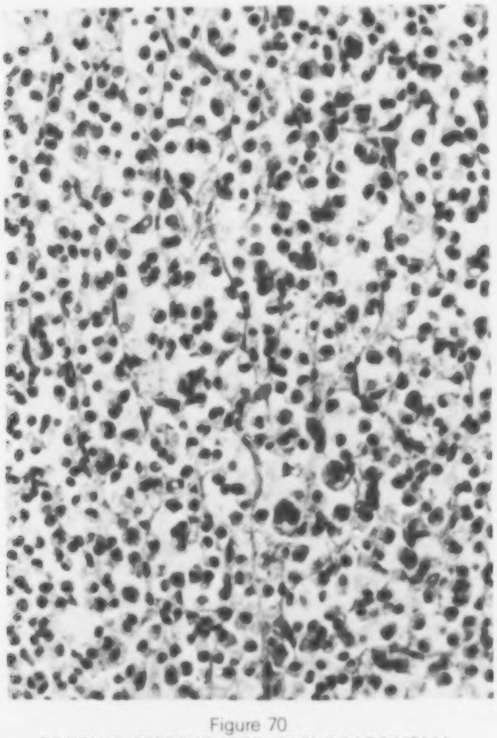

Figure 70
POORLY DIFFERENTIATED ADENOCARCINOMA, SMALL CELL TYPE

Trabeculae and poorly-defined glands are formed by small cells with hyperchromatic nuclei that vary in size. The cytoplasm of many cells contains mucus. This tumor should not be mistaken for an oat cell carcinoma. X250. (Fig. 45 from Fascicle 26, First Series.)

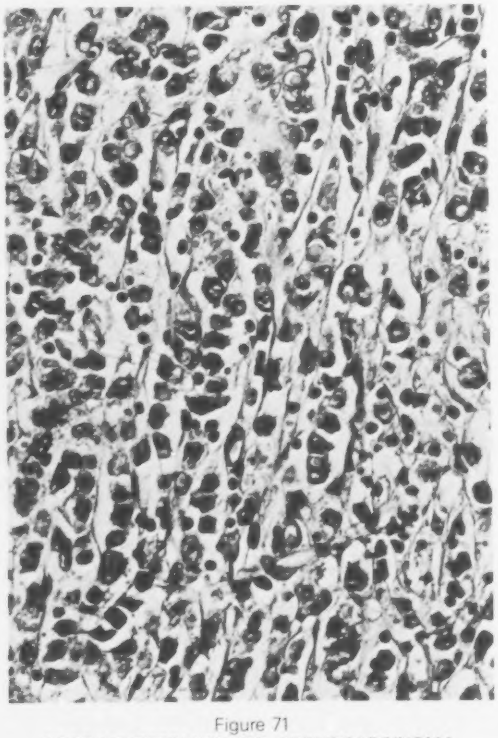

Figure 71
POORLY DIFFERENTIATED ADENOCARCINOMA, SMALL CELL TYPE

Tumor cells arranged in long slender columns have infiltrated the stroma. This pattern, which resembles the Indian file phenomenon, may also occur with other tumor types, especially signet ring cell adenocarcinomas. X330.

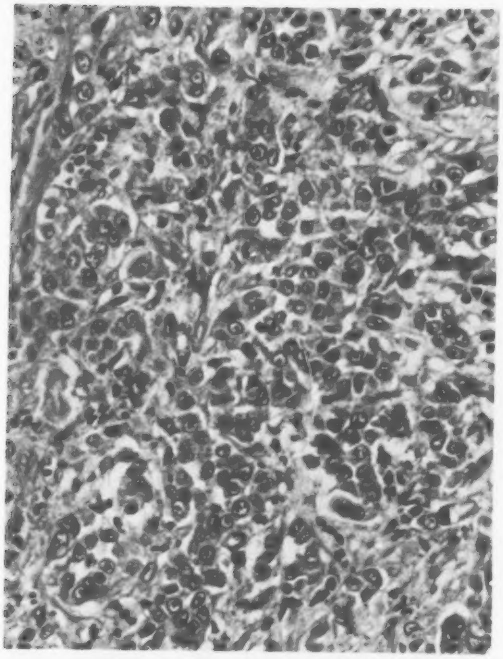

Figure 72
(Figures 72 and 73 from same patient)
POORLY DIFFERENTIATED ADENOCARCINOMA, SMALL CELL TYPE

Neoplastic cells have round nuclei and prominent nucleoli. The cells tend to be arranged in cords. X160.

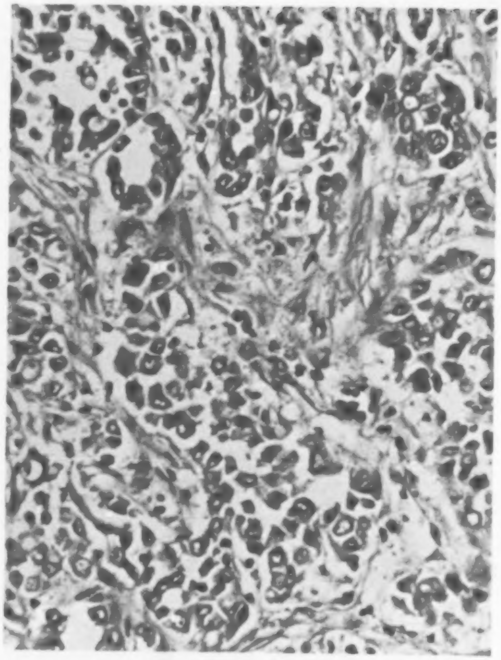

Figure 73
POORLY DIFFERENTIATED ADENOCARCINOMA, SMALL CELL TYPE

This is the same tumor shown in figure 72. In this area, however, the cells seem to form poorly defined glands. X160.

The absence of ribbons, festoons, and pseudorosettes, as well as a lack of spindle cells and secretory granules, differentiate this tumor from oat cell carcinomas. Furthermore, cells from this type of adenocarcinoma tend to be larger than oat cells and often have vesicular nuclei and a mucin containing cytoplasm.

Adenocarcinomas of this type, that is, composed of small cells with vesicular nuclei and prominent nucleoli, can be confused with histiocytic lymphomas. This is most likely to occur with those small cell tumors that grow in solid sheets. The identification of mucin and gland formation excludes a diagnosis of lymphoma.

Signet Ring Cell Adenocarcinoma

As the name indicates, signet ring cells are the predominant, or even the exclusive, element in these tumors. They grow either in cords and sheets or form incomplete glandular structures which usually lie in a mucoid stroma (figs. 74, 75). The Indian file phenomenon can be observed in some areas. Submucosal growth is prominent in some tumors, especially those in which a mucosal lesion is not apparent (fig. 74). Hyperplasia of the mucous glands is also noted in some patients. In a small number of patients, these signet ring cell tumors show areas of a well differentiated adenocarcinoma. Some cells contain CEA.

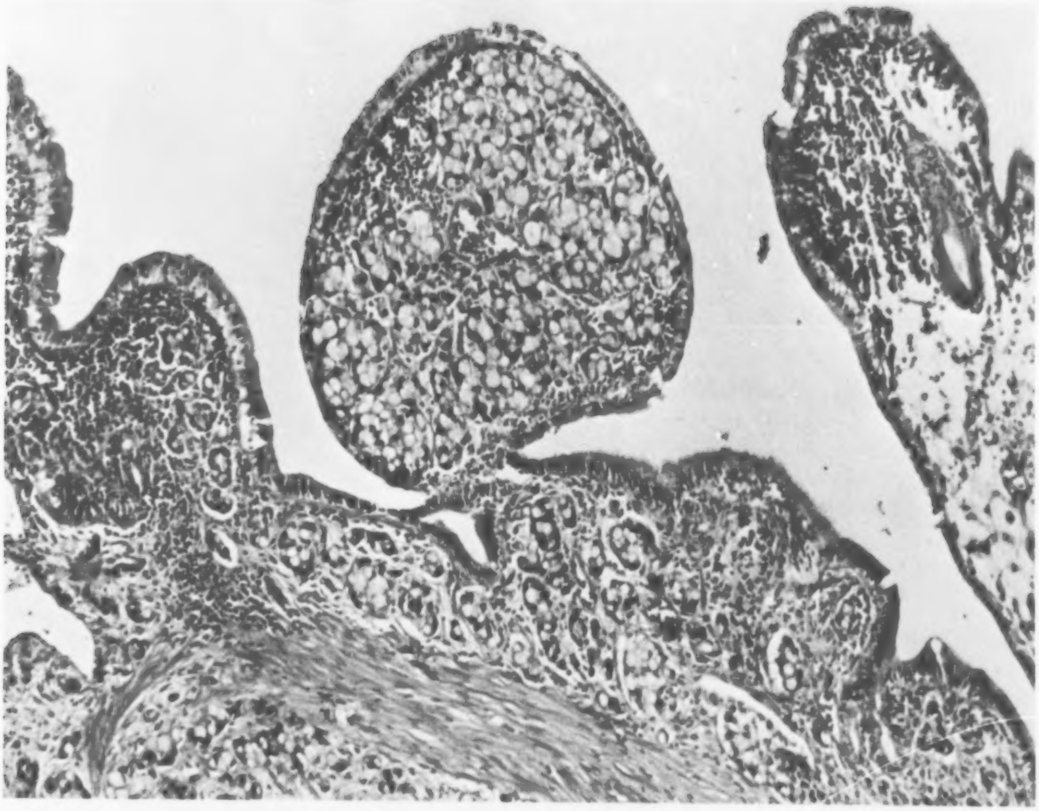

Figure 74
SIGNET RING CELL ADENOCARCINOMA
Tumor cells have infiltrated the lamina propria and muscle coat, leaving the overlying epithelium intact. This type of growth pattern is often seen in signet ring cell adenocarcinomas that diffusely infiltrate the wall of the gallbladder. X100.

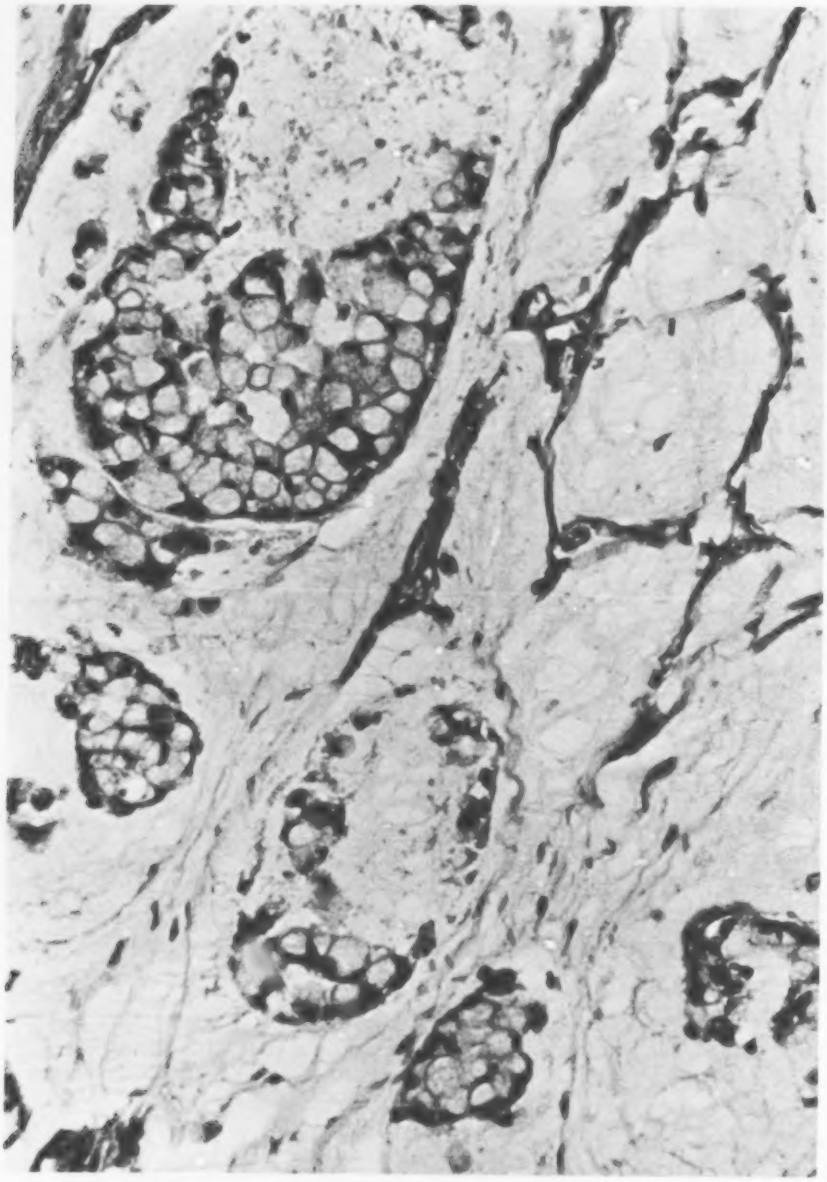

Figure 75
SIGNET RING CELL ADENOCARCINOMA
Small groups of neoplastic signet ring cells lie in a mucoid stroma. X250.

Adenocarcinoma, Clear Cell Type

Although clear cells can represent focal changes in some adenocarcinomas (fig. 76), tumors composed predominantly of clear cells are exceedingly rare and always arouse interest. Recently, we reviewed a case involving the fundus and associated with cholelithiasis. Clear cell carcinomas of the gallbladder have been previously described (Tyson and Piney). A clear cell adenocarcinoma has also been reported in the intrahepatic ducts in a patient with Caroli's disease (Leroy et al.).

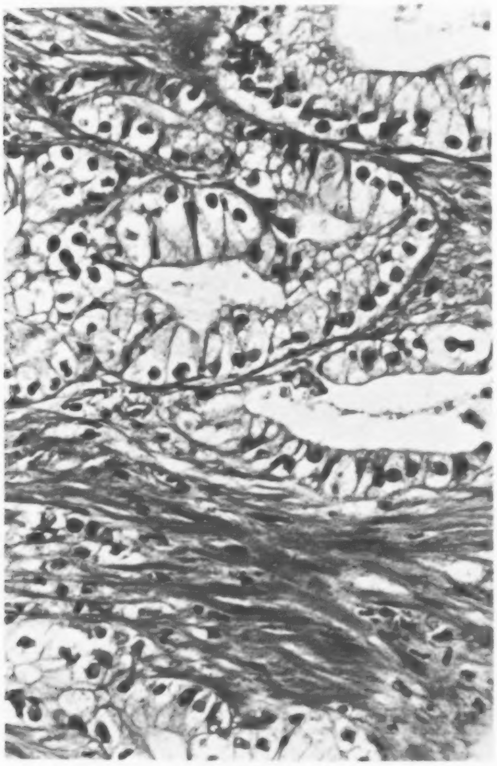

Figure 76
WELL DIFFERENTIATED ADENOCARCINOMA
WITH FOCAL CLEAR CELL CHANGE
Neoplastic glands are lined by columnar cells having a clear cytoplasm and basal nuclei. X200.

Grossly, the tumor we examined was a polypoid and infiltrating nodular mass that was yellow white in color and contained areas of necrosis and hemorrhage (fig. 77). It invaded the full thickness of the wall.

Histologically, the clear cells form solid sheets, trabeculae, or glandular and papillary structures (fig. 78). While the histologic pattern is variable, individual cells are uniform in appearance, being polygonal, cuboidal, or columnar. They have a central or eccentric hyperchromatic nucleus, a clear cytoplasm, and well defined cytoplasmic borders. Slight nuclear pleomorphism and a few mitotic figures are found. The cytoplasm is rich in glycogen as shown by the PAS positive reaction, which becomes negative after diastase digestion. The alcian blue and colloidal iron stains are negative. In our patient, 20 to 30 percent of the tumor also had the pattern of a well differentiated adenocarcinoma with mucin production. In most of the tumor these two components were separated, but in some areas they were mixed (fig. 79).

It is important to separate primary clear cell carcinoma of the gallbladder from a metastatic renal cell carcinoma, which it may resemble (Osman et al.). Although these tumors are similar, the presence of other patterns, especially one of a well differentiated adenocarcinoma with mucin production, supports a diagnosis of a primary tumor in the gallbladder. Also, the presence of severe dysplasia or carcinoma in situ in the adjacent mucosa favors a primary carcinoma in the gallbladder. In small biopsy specimens, showing only the clear cell portion, this separation may not be possible. Another point in the differential diagnosis is the fact that a metastatic lesion may be limited to the muscle layer and perimuscular connective tissue, and not involve the mucosa. Primary tumors usually involve the mucosa. One must also keep in mind that a metastasis to the gallbladder is seldom the first manifestation of a renal cell carcinoma. Even at autopsy, metastatic deposits from carcinoma of the kidney in the gallbladder are rarely seen. The incidence was 0.6 percent in one large series (Bennington and Kradjian).

Clear cell carcinomas of other organs, such as those from the ovary, lung, skin, or salivary glands, should also be considered in the differential diagnosis; however, to our knowledge, no metastases to the gallbladder from these tumors have been reported.

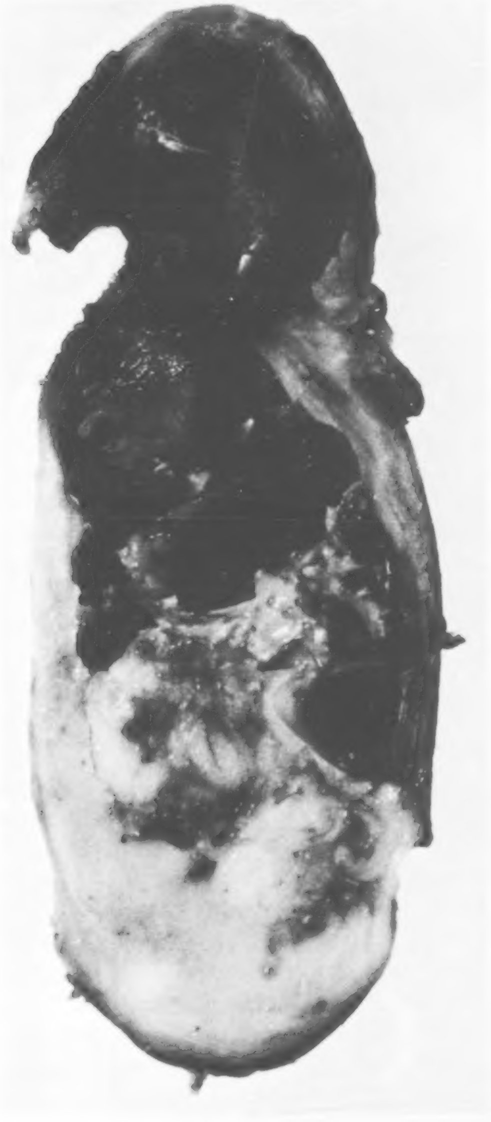

Figure 77
ADENOCARCINOMA, CLEAR CELL TYPE
A polypoid tumor arising in the fundus of the gallbladder shows areas of hemorrhage and necrosis. Two calculi are seen. Grossly, this tumor is similar to other carcinomas of the gallbladder.

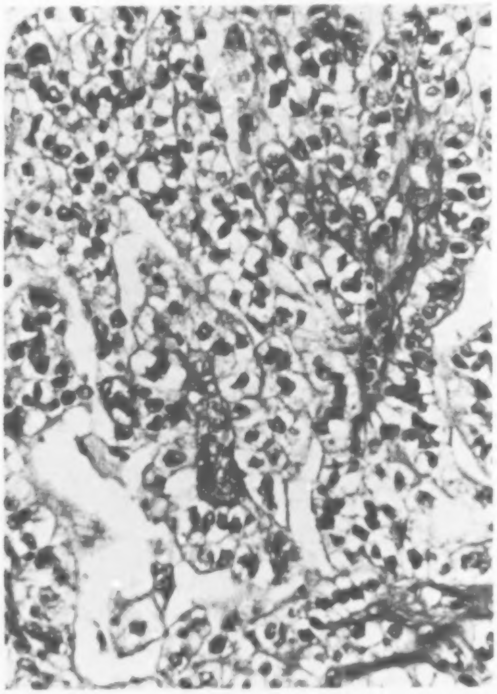

Figure 78
ADENOCARCINOMA, CLEAR CELL TYPE
The columnar and polygonal tumor cells have a clear cytoplasm and sharply defined cytoplasmic borders. They are arranged either in cords or as poorly defined glandular structures. X180.

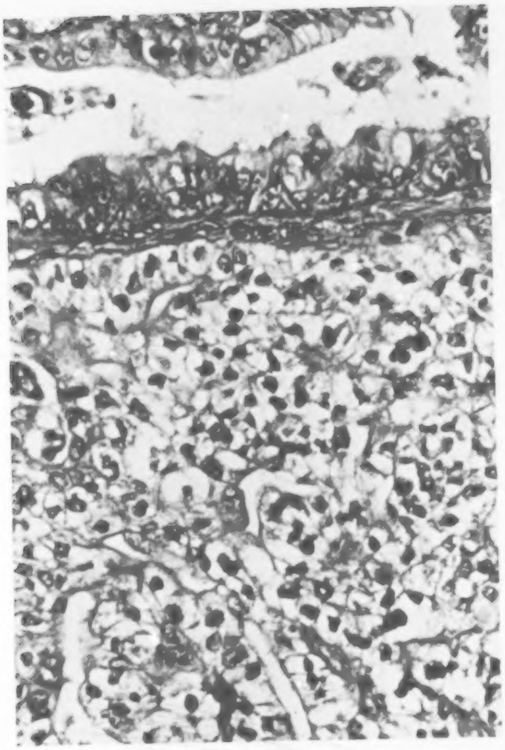

Figure 79
ADENOCARCINOMA, CLEAR CELL TYPE
A neoplastic gland which is characteristic of a well differentiated adenocarcinoma is seen in the upper part of the photomicrograph. Beneath these glands, the tumor consists of clear cells. X180.

Adenocarcinoma with Choriocarcinoma-like Areas

There was one unusual tumor in our series which should be mentioned, since similar lesions have also been reported in the esophagus (McKechnie and Fechner), stomach (Tanaka; Wurzel and Brooks; Saigo et al.), jejunum (Soresi), and colon (Park and Reid). This tumor was an adenocarcinoma that contained choriocarcinoma-like elements. The glandular component was well differentiated; that is, most glands were well formed and lined by tall uniform columnar cells. Some contained multinucleated giant cells in their lumen (fig. 80). In addition, solid cords and trabeculae with a central mass of cytotrophoblastic-like neoplastic cells surrounded by syncytiotrophoblastic cells infiltrated the stroma (fig. 81). Extensive necrosis was noted, but not of the hemorrhagic type seen in the typical gonadal or uterine choriocarcinoma.

Colloid Carcinoma

SYNONYMS AND RELATED TERMS: Mucinous carcinoma.

This tumor, which is uncommon, representing 4 percent of all malignant types in our material, is identical to that found in the breast and other sites. It is characterized by small clusters of malignant epithelial cells surrounded by large deposits of extracellular mucin (fig. 82). The mucin, which dominates the histological picture, usually stains basophilic. Very often, the mucous pools, especially the larger ones, are surrounded by fibrous septae. In general, there are few glandular elements, and, when present, they are often distended with mucin. The malignant cells have compressed peripheral nuclei and a cytoplasm engorged with mucin.

A diagnosis of colloid carcinoma should be suspected from gross examination when large amounts of mucus are found in the primary tumor.

Because colloid carcinomas are uncommon, we have not been able to compare their clinical behavior or modes of spread with other types of carcinomas of the gallbladder. It was reported in the previous Fascicle that these tumors are more apt to spread to the peritoneum than other histologic types. Some well differentiated adenocarcinomas may show areas of excessive

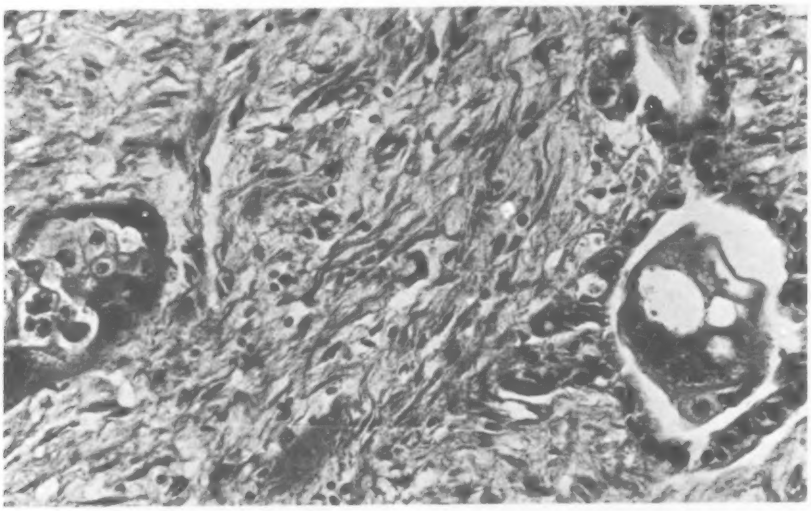

Figure 80

ADENOCARCINOMA WITH CHORIOCARCINOMA-LIKE AREAS

Floating in the gland lumen is a multinucleated giant cell with vacuolated cytoplasm. Another syncytiotrophoblast-like cell is seen in the stroma. X250.

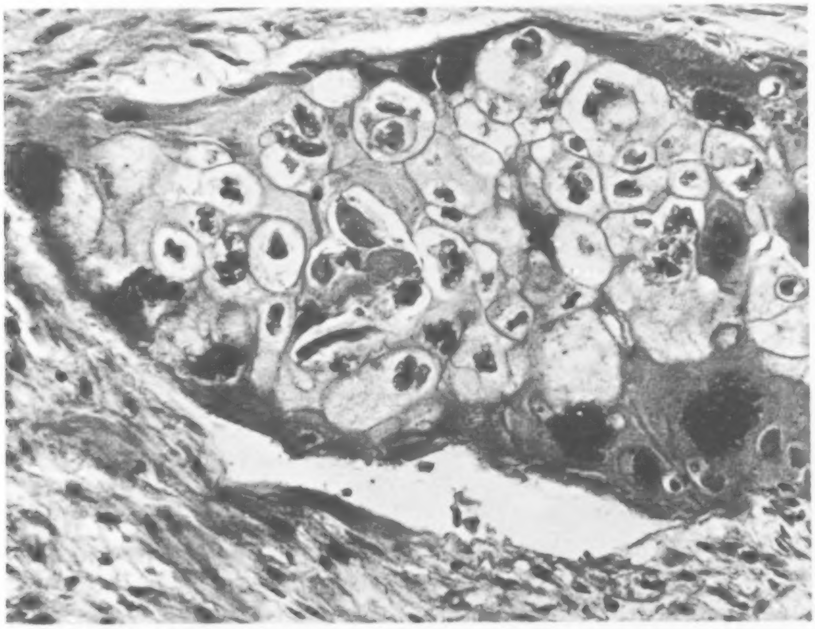

Figure 81

ADENOCARCINOMA WITH CHORIOCARCINOMA-LIKE AREAS

Neoplastic syncytiotrophoblastic-like cells surround a group of cells with cytotrophoblastic-like features. In other areas, this tumor showed the pattern of a well differentiated adenocarcinoma. X350.

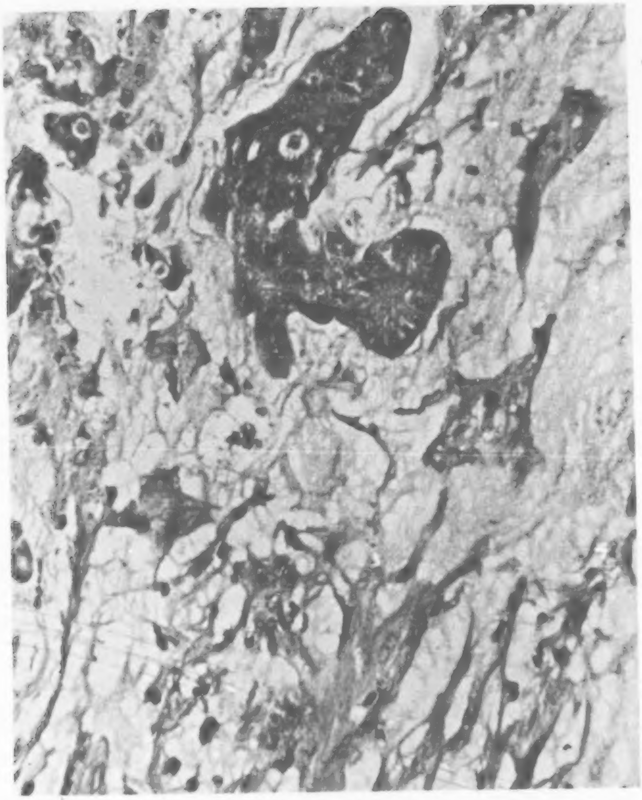

Figure 82
COLLOID CARCINOMA
A small group of neoplastic cells lies in a pool of basophilic mucin. X180.

mucous production, however, unless extracellular mucin deposits are the predominant feature, these tumors should not be labeled as colloid or mucinous carcinomas.

Squamous Cell Carcinoma

SYNONYMS AND RELATED TERMS: Epidermoid carcinoma.

This tumor probably arises in areas of squamous metaplasia of the surface epithelium. In two of the four patients in our series, we were able to demonstrate squamous metaplasia, dysplasia, and carcinoma in situ in the mucosa adjacent to the invasive cancer (fig. 83). As with squamous cell carcinomas in other sites, the tumor consists of cords, islands, or sheets of malignant squamous cells separated by a dense fibrous stroma. The extent of differentiation of the squamous cells can vary from the anaplastic to the mature keratinizing type (figs. 84, 85). CEA is present in the neoplastic squamous cells.

The spindle cell variant of squamous carcinoma can also occur in the gallbladder. However, it is not possible, in many patients, to separate this tumor from a carcinosarcoma with hematoxylin and eosin

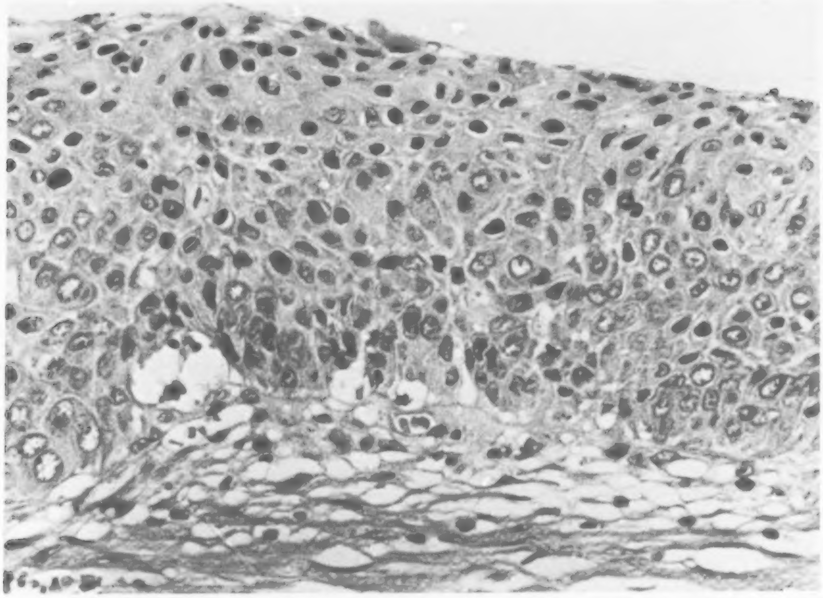

Figure 83
SQUAMOUS DYSPLASIA
The gallbladder epithelium has been replaced by squamous cells that show nuclear atypia. X250.

stained sections alone. The presence of epithelial markers, such as keratin, in the spindle cells is the only way to establish whether the lesion is of squamous origin.

We must caution, however, that multiple sections must be examined before a diagnosis of pure squamous cell carcinoma is issued, because some adenosquamous carcinomas have a prominent squamous cell component. Squamous cell carcinomas are not common; they constituted only 1 percent of all tumors in our series.

Adenosquamous Carcinoma

SYNONYMS AND RELATED TERMS: Adenoacanthoma; mucoepidermoid carcinoma.

This type is similar to that seen in other organs. It consists of a variable mixture of two malignant but different histologic components, one glandular and the other squamous (fig. 86). The squamous component may be scattered, focal, or occupy large areas of the tumor. It may be mixed

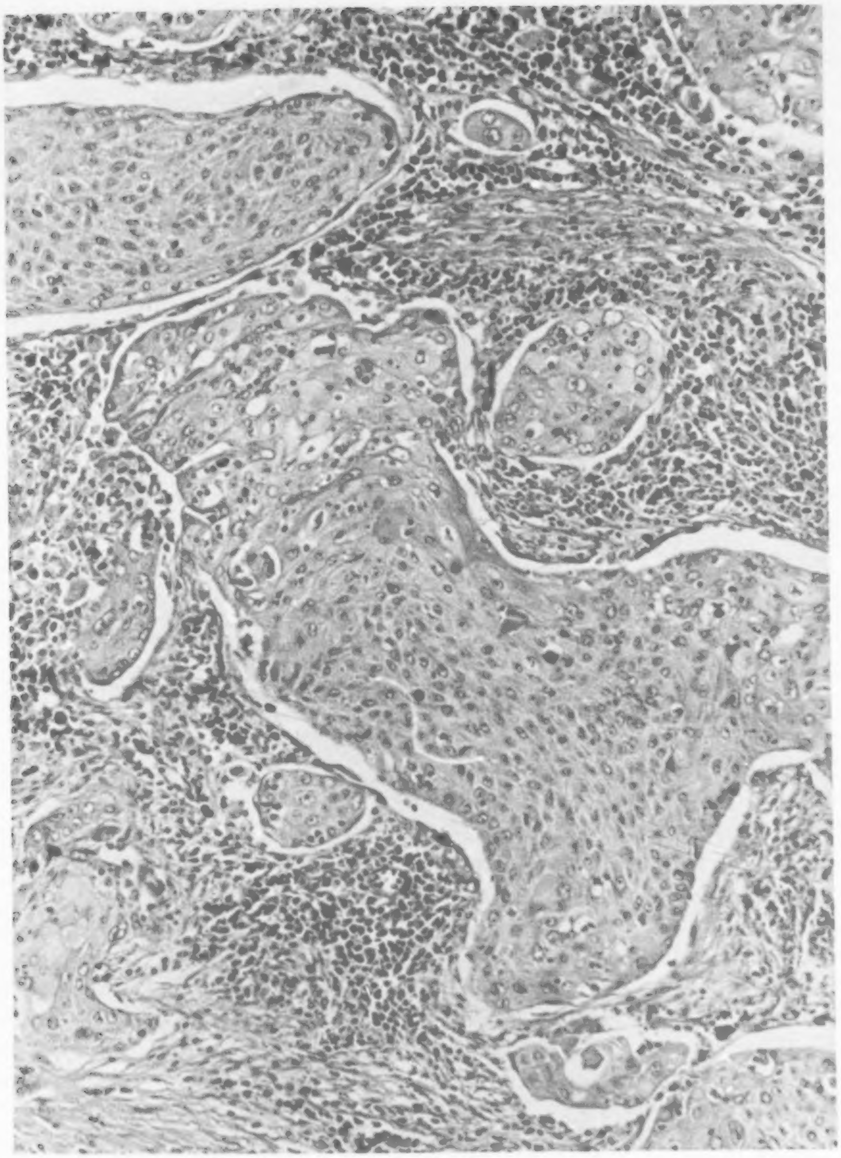

Figure 84
SQUAMOUS CELL CARCINOMA
Anastomosing cords of neoplastic squamous cells are infiltrating the stroma, which contains some chronic inflammatory cells. X160.

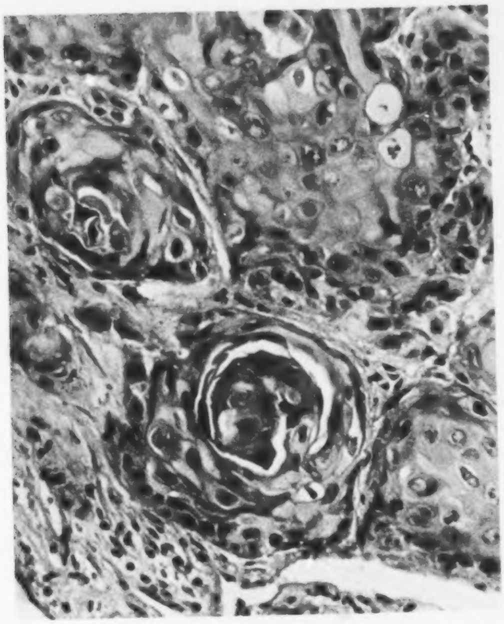

Figure 85
SQUAMOUS CELL CARCINOMA
Keratin pearls are evident in this photograph. X200.

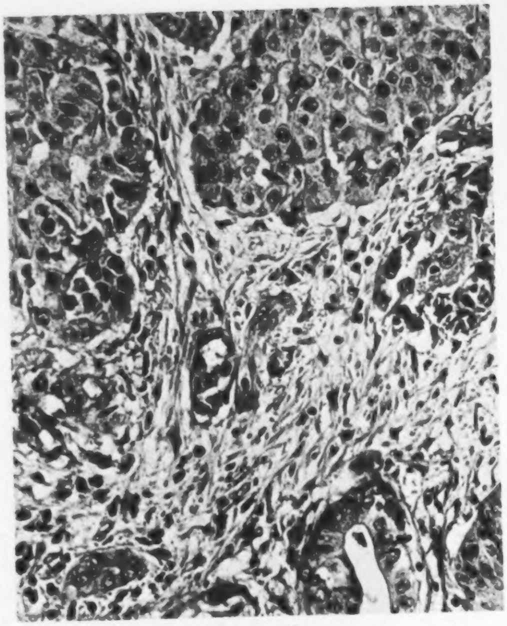

Figure 86
ADENOSQUAMOUS CARCINOMA
A fibrous stroma separates sheets of nonkeratinizing neoplastic squamous cells from several glandular structures. X180.

with glandular epithelium or appear independent from the glands separated by stroma (fig. 87). The degree of differentiation of these two elements varies from tumor to tumor, but, in general, they tend to be moderately differentiated. Whorls, keratohyalin, or keratin pearls are often present. Only a few tumors show poorly-differentiated or anaplastic features in the squamous cell component. Both the glandular and squamous components contain carcinoembryonic antigen.

Adenosquamous carcinomas are not a mixture of two cell lines, each with a separate phenotype that is squamous or glandular, but result from the instability of differentiation of a single cell line; the neoplastic cells are able to express both phenotypes (Steele and Nettesheim).

Oat Cell Carcinoma

SYNONYMS AND RELATED TERMS: Anaplastic carcinoid; malignant carcinoid; small cell anaplastic carcinoma; small cell carcinoma; small cell undifferentiated carcinoma.

This tumor is found in many organs, including the lung, stomach, and pancreas. It is composed of small cells, most of which appear undifferentiated with the light microscope, although at the ultrastructural level a few neoplastic cells will show endocrine differentiation, as revealed by the presence of neurosecretory granules. Because of the presence of neurosecretory granules, a histologic similarity to carcinoids, hormonal peptide secretion, and occasional association with endocrine syndromes, some investigators have considered oat cell carcinomas as the ana-

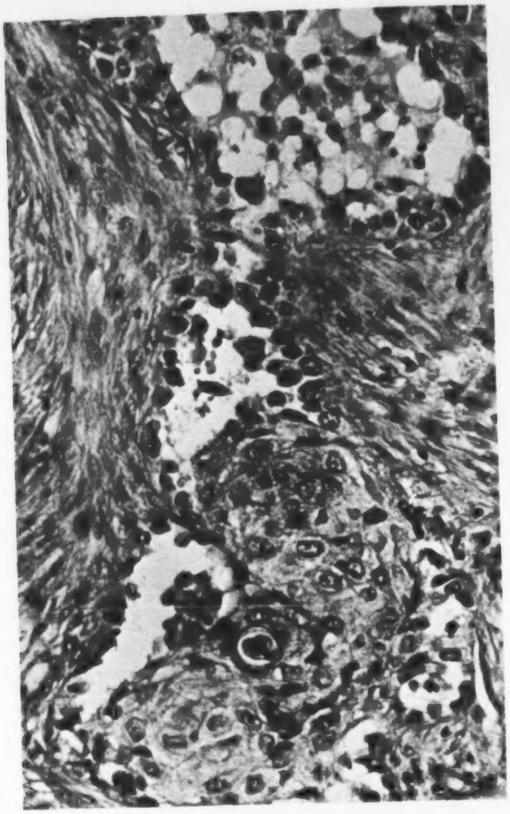

Figure 87
ADENOSQUAMOUS CARCINOMA
Malignant squamous cells filling the lumen of a neoplastic gland lined by cuboidal cells. Even though the stroma shows fibroblastic proliferation, this tumor is not a carcinosarcoma because the stroma is not malignant. X200.

plastic variant of a carcinoid tumor. Moreover, the existence in the gallbladder, as in the lung, of an atypical or intermediate carcinoid tumor, which is thought to be a link between the well differentiated carcinoid and oat cell carcinoma, strengthens this concept.

In view of the secretion of hormonal peptides, some authors have expressed the opinion that oat cell carcinomas belong to the family of amine precursor uptake decarboxylase tumors, or APUDomas, and that they are of neural crest origin. Convincing evidence for such an origin, however, is lacking. On the contrary, the presence of two elements in some tumors – the well differentiated glands and small cells – suggests that both components arise from a common tumor cell of endodermal derivation capable of differentiating in two directions, endocrine and glandular. In addition, the presence of membrane bound granules and well developed microvilli in some tumor cells in one of our cases further supports the concept of dual differentiation.

The clinical and epidemiologic features of patients with oat cell carcinomas are similar to those of other carcinomas of the gallbladder (Albores-Saavedra et al., 1984). Oat cell carcinomas are more common in females, are almost always associated with stones, and have a poor prognosis. Only one of our 18 patients survived 11 months following cholecystectomy, radiotherapy, and chemotherapy. These tumors also have the ability to produce certain hormonal peptides. A patient with Cushing's syndrome, which we believe was associated with oat cell carcinoma of the gallbladder, has been reported (Spence and Burns-Cox).

The histologic spectra of oat cell carcinomas of the gallbladder are comparable to that of the corresponding lung tumors. The tumor is composed of small round cells, usually mixed with spindle cells (figs. 88, 89). Multinucleated giant cells are uncommon, occurring in less than 10 percent of the cases. Both the round and spindle cells have hyperchromatic nuclei, finely dispersed chromatin, and inconspicuous nucleoli. The cytoplasm is sparse, eosinophilic, and of imprecise limits. These cells are either arranged in compact sheets or

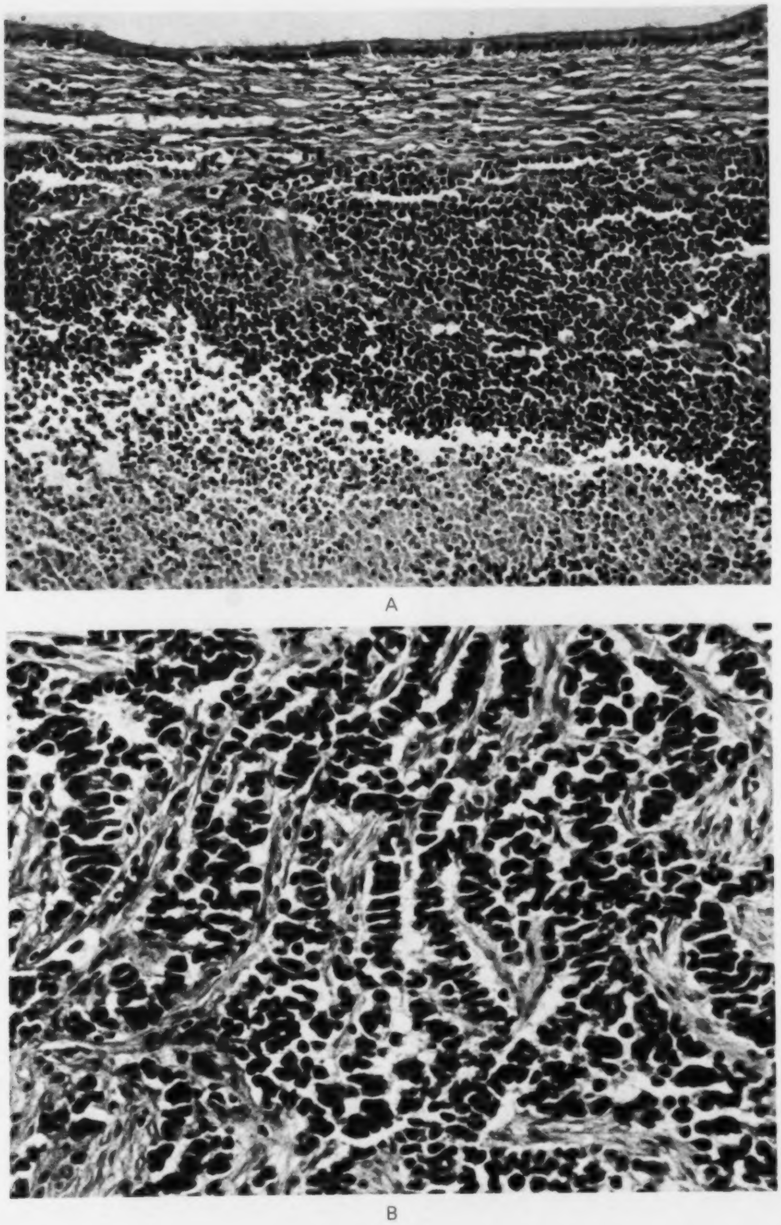

Figure 88
OAT CELL CARCINOMA

(A) Tumor cells are small, round, and hyperchromatic. The tumor exhibits submucosal growth, which is characteristic of oat cell carcinomas. Extensive necrosis has occurred. X160. (B) This is the same tumor shown in (A). In this field, however, most neoplastic cells are arranged in ribbons and festoons. X250.

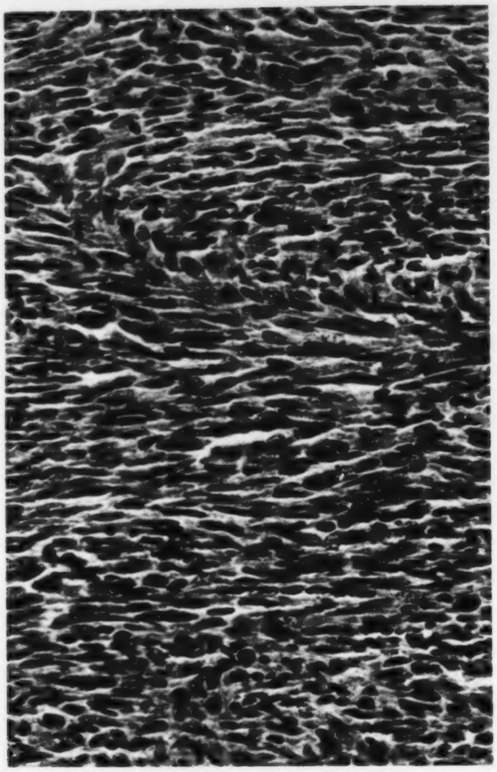

Figure 89
OAT CELL CARCINOMA
This oat cell carcinoma is composed predominantly of spindle cells. X330.

divided into small irregular nests by thin bands of connective tissue. In almost every tumor we have examined, there were also areas in which the cells formed cords, trabeculae, and festoons (fig. 90). Tubular structures are rare. Central necrosis of the cords often results in a comedocarcinoma-like pattern (fig. 91). In areas of extensive necrosis, which are present in almost every tumor, the only viable appearing tumor cells are those surrounding blood vessels. In contrast to some oat cell carcinomas in the lung, these vessel walls rarely exhibit the deep basophilic staining which is the result of DNA deposition. In one of our patients, the gallbladder epithelium overlying the tumor showed dysplastic changes and carcinoma in situ, but cells from these lesions had no resemblance to those of the infiltrating oat cell carcinoma. Furthermore, if adequately sampled, foci of well differentiated neoplastic glands can be demonstrated in 25 percent of these tumors. These foci of neoplastic glands are usually confined to a few areas, but in some tumors they may be a major component.

Grimelius stain may reveal fine argyrophil granules in an occasional tumor. In our series of 18 oat cell carcinomas of the gallbladder, only three were focally positive with the Grimelius stain. With the immunoperoxidase technic, carcinoembryonic antigen is seen in the neoplastic glands of the combined type and in focal areas of a small percentage of pure oat cell carcinomas. By electron microscopy, a few neurosecretory granules are also seen in some of the neoplastic cells.

Oat cell carcinomas can be confused with malignant lymphomas. However, the presence of cords, ribbons, and festoons allows a distinction. In addition, cells from these anaplastic carcinomas have very hyperchromatic nuclei, more cytoplasm, and are larger than lymphocytes. Also, the latter cells do not show the nuclear spindling, neurosecretory granules, and cell junctions that characterize oat cell carcinomas. The criteria used to distinguish atypical carcinoid tumors from oat cell carcinomas of the lung can also be applied to the differential diagnosis of these tumors in the gallbladder. Briefly, atypical carcinoids appear as a small submucosal nodule and show a more organoid pattern than oat

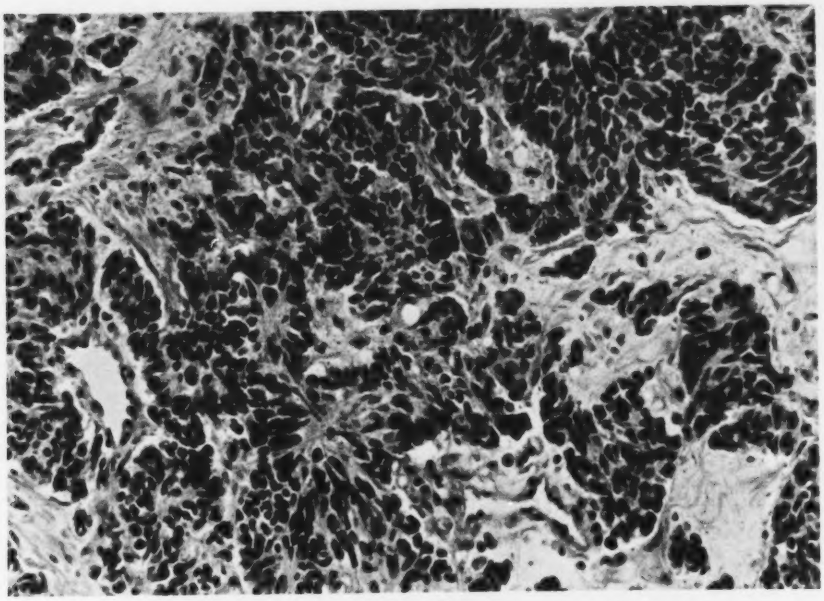

Figure 90
OAT CELL CARCINOMA
Anastomosing cords of spindle cells separated by fibrosis. A pseudorosette is seen. X200.

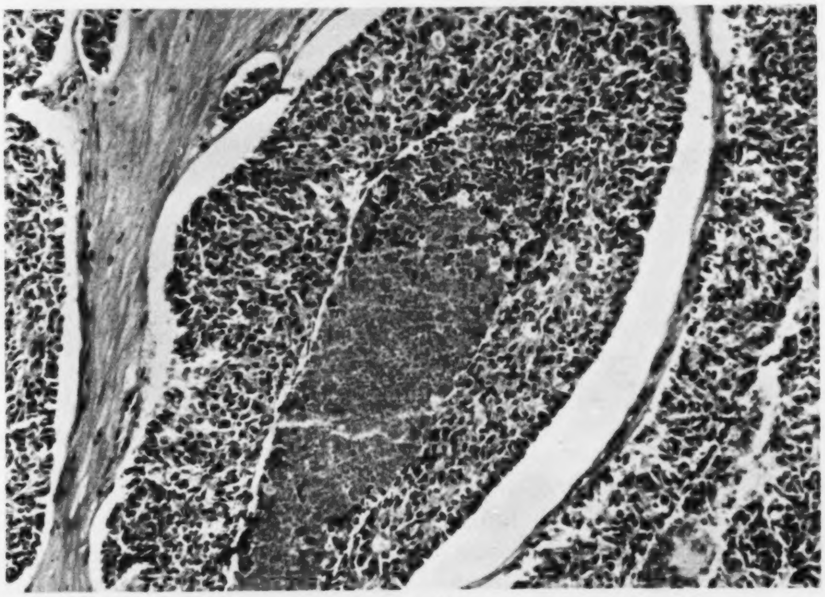

Figure 91
OAT CELL CARCINOMA
Central necrosis of a cord of neoplastic cells has caused a comedocarcinoma pattern in this oat cell carcinoma. X150.

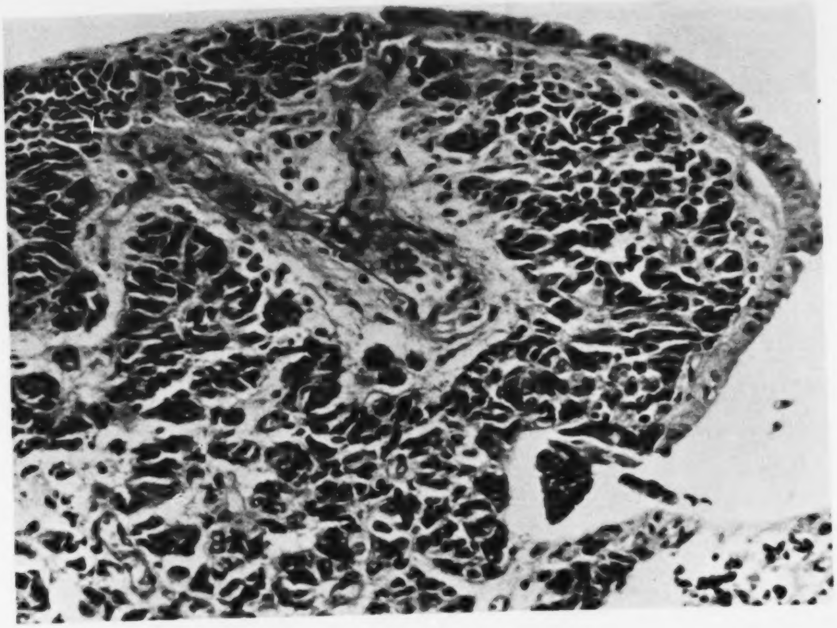

Figure 92
(Figures 92 and 93 from same patient)
ATYPICAL CARCINOID TUMOR
Although cytologically similar to oat cell carcinomas, this tumor exhibits more ribbons and festoons, less necrosis, and fewer mitotic figures than oat cell carcinomas. Dysplastic changes are seen in the overlying epithelium. X180.

cell carcinomas (figs. 92, 93; pl. II-D). In fact, in some areas the pattern can still be recognized as that of a carcinoid tumor. In addition, the atypical carcinoid lacks necrosis, has few mitotic figures and, more importantly, follows a less aggressive clinical course than that of oat cell carcinoma. The differential diagnosis with poorly differentiated small cell adenocarcinoma is discussed on page 75. In metastatic deposits it is not possible to separate oat cell carcinomas of the gallbladder from those originating in other sites.

Oat cell carcinomas of the gallbladder are probably more common than reported in the literature. Only four patients interpreted as having malignant carcinoid tumors have been recorded (Vaittinen; Bosl et al.), but in our series of 386 gallbladder cancers, we found 18, or 4.7 percent. In fact, they are more common than pure squamous cell carcinomas of the gallbladder. We also believe that some oat cell carcinomas have been reported as undifferentiated or anaplastic carcinomas. Finally, oat cell carcinomas should not be confused with the small cell undifferentiated adenocarcinomas that also occur in the gallbladder.

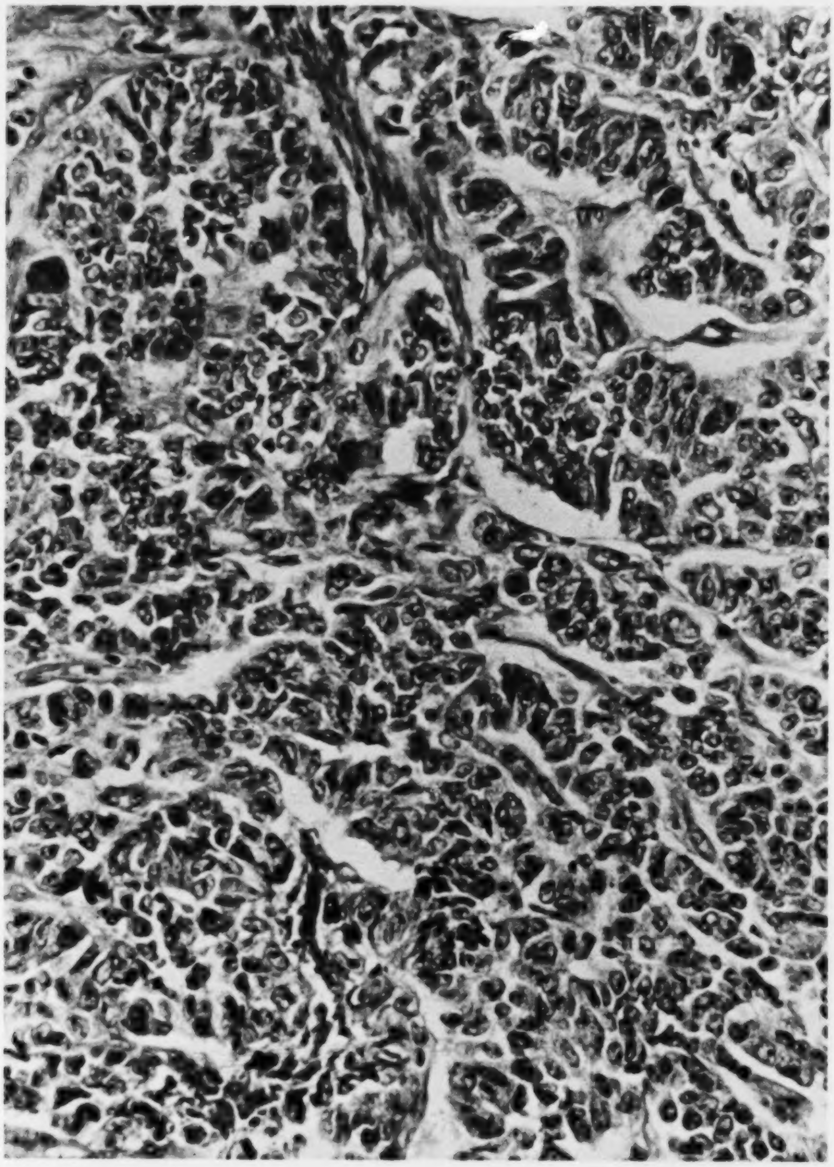

Figure 93
ATYPICAL CARCINOID TUMOR
In this area of the tumor shown in figure 92, the tumor appears more differentiated than oat cell carcinomas, resembling the classic carcinoid. There is no necrosis and no mitotic figures. X200.

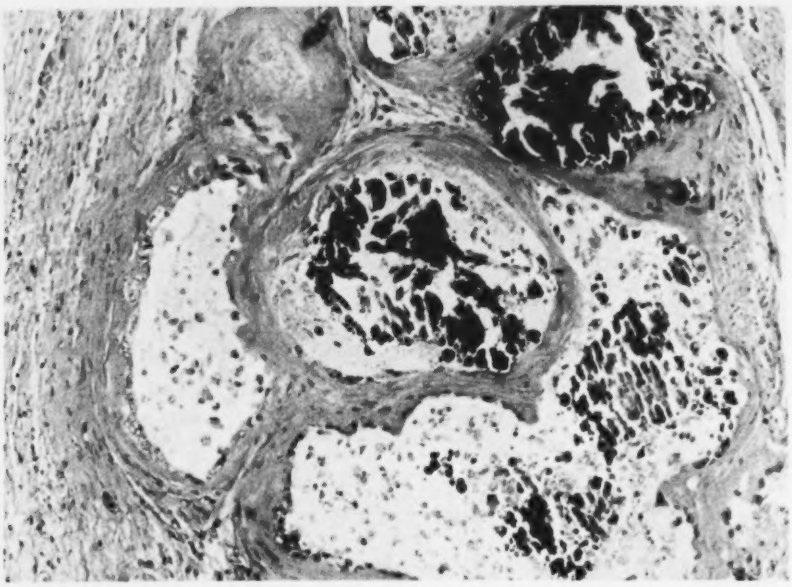

Figure 94
CALCIFICATION IN WELL DIFFERENTIATED ADENOCARCINOMA
Neoplastic glands in the wall of the gallbladder contain precipitated calcium. As a rule, in cases of calcification, the epithelial lining is poorly preserved and the glands are surrounded by a ring of dense hyalinized fibrous tissue. X100.

CALCIFICATION

Occasionally, calcium precipitates in the mucus that accumulates in the lumen of the neoplastic glands (Parker and Joffe; fig. 94). This calcium, which is often visible on radiographs, is a diagnostic help to the radiologist, although similar calcium deposits can occur in carcinomas of the stomach or colon. Calcification occurs in less than 1 percent of all patients with gallbladder carcinomas. It is usually found in those tumors that are well differentiated (Rogers et al.).

ULTRASTRUCTURE

Electron microscopic studies on gallbladder neoplasms are virtually nonexistent. As a result, the following description is primarily based on a series of carcinomas that we have examined (Larraza-Hernadez et al.). In this section we describe the ultrastructural features that seem to have diagnostic or histogenetic importance and stress similarities and differences with normal cells.

The ultrastructure of a well differentiated adenocarcinoma of the gallbladder resembles, to some degree, normal gallbladder epithelium. Thus, two of the three epithelial cell types found in the normal human gallbladder are present – the ordinary columnar cell and the pencil-like cell (fig. 95). The third cell type, the basal cell, was not identified in any of the tumors that we examined, nor was it mentioned in the only published ultrastructural study on gallbladder adenocarcinoma (Marcus et al.). As in normal epithelium, these two cell types rest on a basal lamina which, in the case of tumors, may be thickened or even duplicated.

The predominant neoplastic cell, the ordinary light columnar cell, has a large central or basal nucleus which may be round, ovoid, irregular, or elongated. The nuclei, which occasionally show multiple indentations, contain coarse marginal chromatin and one or two nucleoli. Functionally, these columnar cells usually show evidence of excessive mucin secretion. They contain either multiple small mucin droplets or large coalescent vacuoles that occupy most of the cytoplasm (fig. 96). Intracytoplasmic lumen formation is occasionally seen. Microvilli emerge from the apical surface and project into the gland lumen. Their height and morphology vary; most are short and blunt, while others are tall and slender.

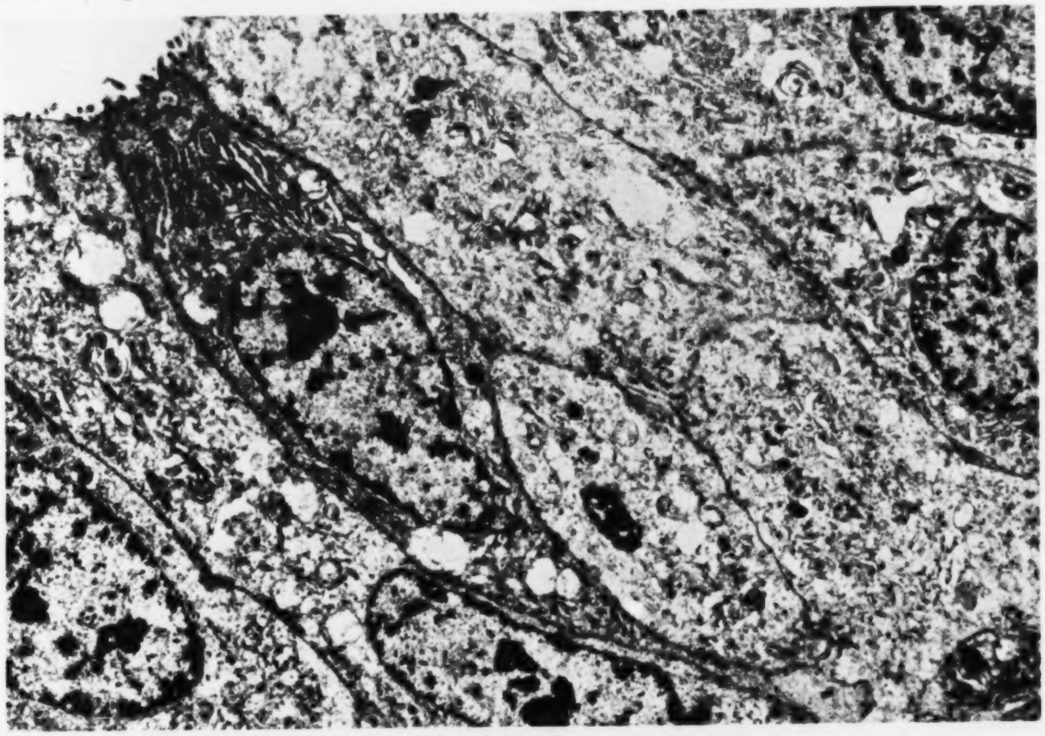

Figure 95
ULTRASTRUCTURE – ADENOCARCINOMA
Neoplastic columnar and pencil-like cells are seen in a well differentiated adenocarcinoma. The columnar cells contain mucus droplets and are covered by microvilli. The pencil-like cell is darker, tapers toward the basal lamina, and has a prominent rough endoplasmic reticulum located above the nucleus. Short microvilli cover the surface. X5400.

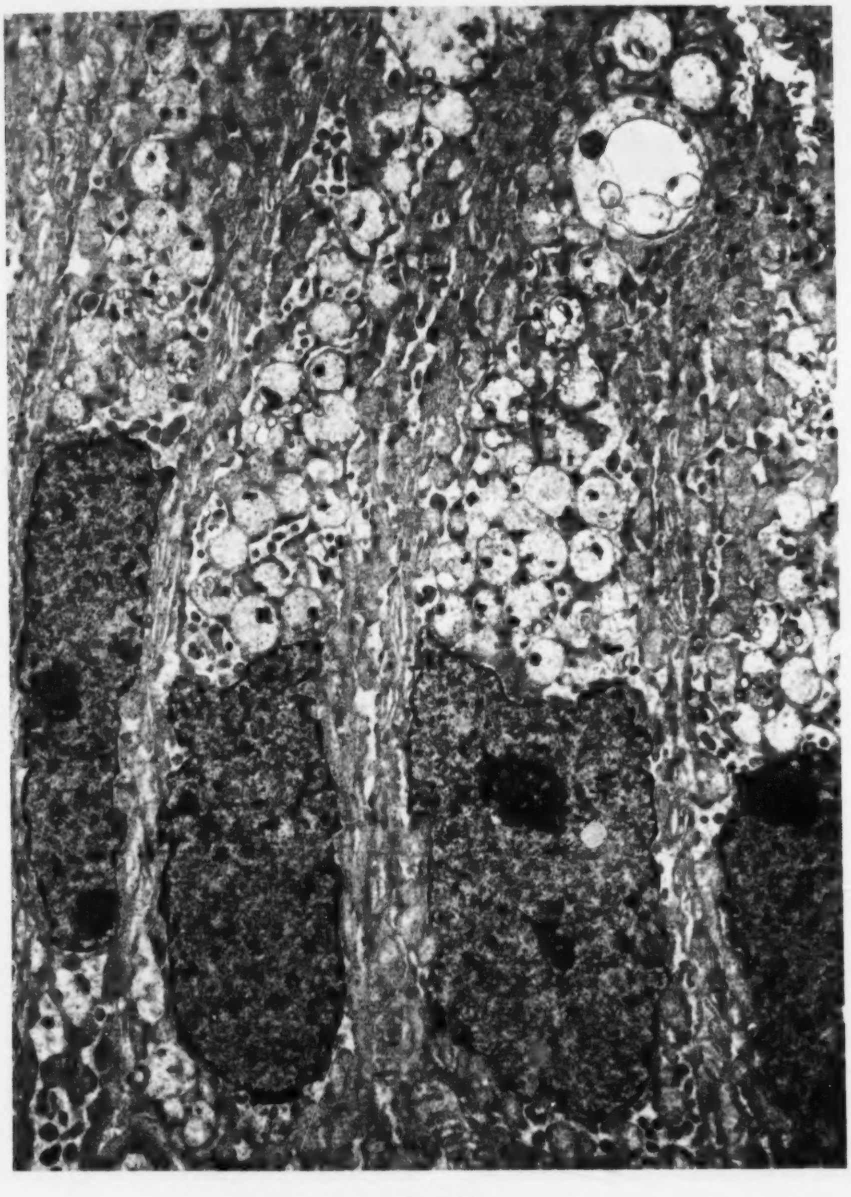

Figure 96
ULTRASTRUCTURE – ADENOCARCINOMA
Neoplastic columnar cells show basal nuclei, prominent nucleoli, and numerous mucous vacuoles. X5400.

One well differentiated adenocarcinoma in our series showed focal intestinal metaplasia characterized by a well defined brush border produced by uniform slender and closely spaced microvilli. These microvilli contained microfilament bundles which were continuous with those of the adjacent cytoplasm, the so-called microvillous core rootlets (Marcus et al.). Part of these microvilli were covered with a filamentous glycocalyx. Round or oval membrane-bound structures known as glycocaliceal bodies were seen above and between the microvilli, especially those with core rootlets (fig. 97). These glycocaliceal bodies have a focal or diffuse distribution and a diameter less than 25 percent of individual microvilli. Unfortunately, these two distinct microvilli-related structures (microvillous core rootlets and glycocaliceal bodies) are not specific, since they are identical to those found in some adenocarcinomas of the stomach,

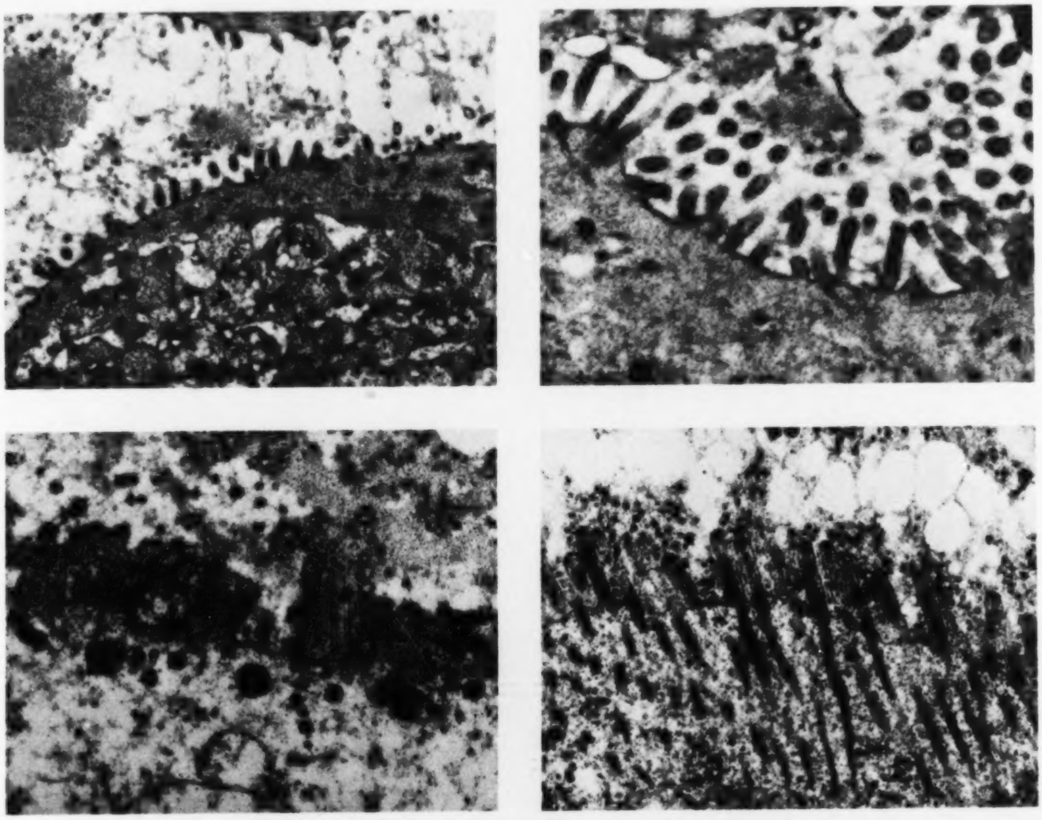

Figure 97
ULTRASTRUCTURE – ADENOCARCINOMA

Four different types of microvilli found in a well differentiated adenocarcinoma are illustrated. The top panels reveal small and poorly developed microvilli, while the lower panels show well developed intestinal-type microvilli. In addition, dark electron dense cytoplasmic bodies are present in the left lower picture. Closely spaced microvilli, with core rootlets and glycocaliceal bodies above and between the microvilli, are seen in the right lower photograph. Top left: X7200. Top right: X15,390. Lower photographs: X19,200.

intestine (Hickey and Seiler), pancreas, lung, ovary, and cervix. As a consequence, we believe their diagnostic value is limited.

The cytoplasmic organelles include a variable number of mitochondria, a well developed rough endoplasmic reticulum, and a Golgi apparatus. Pinocytic vesicles are absent along the apical cytoplasmic surface.

The apical portions of the lateral walls of adjacent tumor cells are connected by junctional complexes. These walls, which may show complex infoldings, are separated by intercellular spaces which in normal cells are considered important for fluid transport.

Pencil-like cells are rarely seen. Located between columnar cells, they extend from the basement lamina to the lumen, although sometimes they do not reach the lumen or the basal lamina. Their dark appearance, narrow profile, well developed supranuclear rough surface endoplasmic reticulum, and minimal mucin content allow easy separation from ordinary columnar cells (fig. 95). The apical surface contains short and scattered microvilli while the opposite end becomes attenuated, resulting in a slender cytoplasmic process which penetrates between columnar cells. Cytoplasmic projections extending to the basal lamina were not seen, a feature usually found in normal pencil-like cells.

Although the pencil-like cell is considered a modified columnar cell, its function in normal and pathologic conditions remains to be determined. Its extensive supranuclear granular endoplasmic reticulum and its presence in malignant tumors do not support the hypothesis that it is a degenerate or inactive cell (Evett et al.).

In the well differentiated adenocarcinoma showing focal intestinal metaplasia, we also identified a few endocrine cells containing round and pleomorphic dense core secretory granules. These cells have a suprabasal location and are similar to the enterochromaffin cells and enterochromaffin-like cells described in association with the intestinal metaplasia of chronic cholecystitis. Their presence in areas of intestinal metaplasia, even when occurring in adenocarcinomas, is interesting but unclear, because their origin, secretory products, and function are unknown.

Epithelial cells with intracytoplasmic lumina which displace the nucleus and cytoplasmic structures toward the periphery characterize the signet ring cell carcinoma (figs. 98, 99). The nuclei are large, ovoid, or reniform and usually contain a single prominent nucleolus. When visible, the endoplasmic reticulum and Golgi apparatus are well developed. Adenosquamous carcinomas are composed of variable proportions of three cell types: one purely squamous, another with glandular features, and a third with a dual differentiation, that is, with tonofilament bundles, mucin droplets, intracytoplasmic lumens, and microvilli (fig. 100).

The most important markers for oat cell carcinomas of the gallbladder are the dense core secretory granules (fig. 101). Two types are found – the small round granules which predominated and the pleomorphic granules. The former are similar to those found in oat cell carcinomas of the lung, whereas the latter are similar to those seen in EC cells of the gallbladder mucosa associated with intestinal metaplasia. We have not seen mucous granules or tonofilament bundles in oat cells from the gallbladder, even though these structures have been found in oat cell carcinomas from other sites.

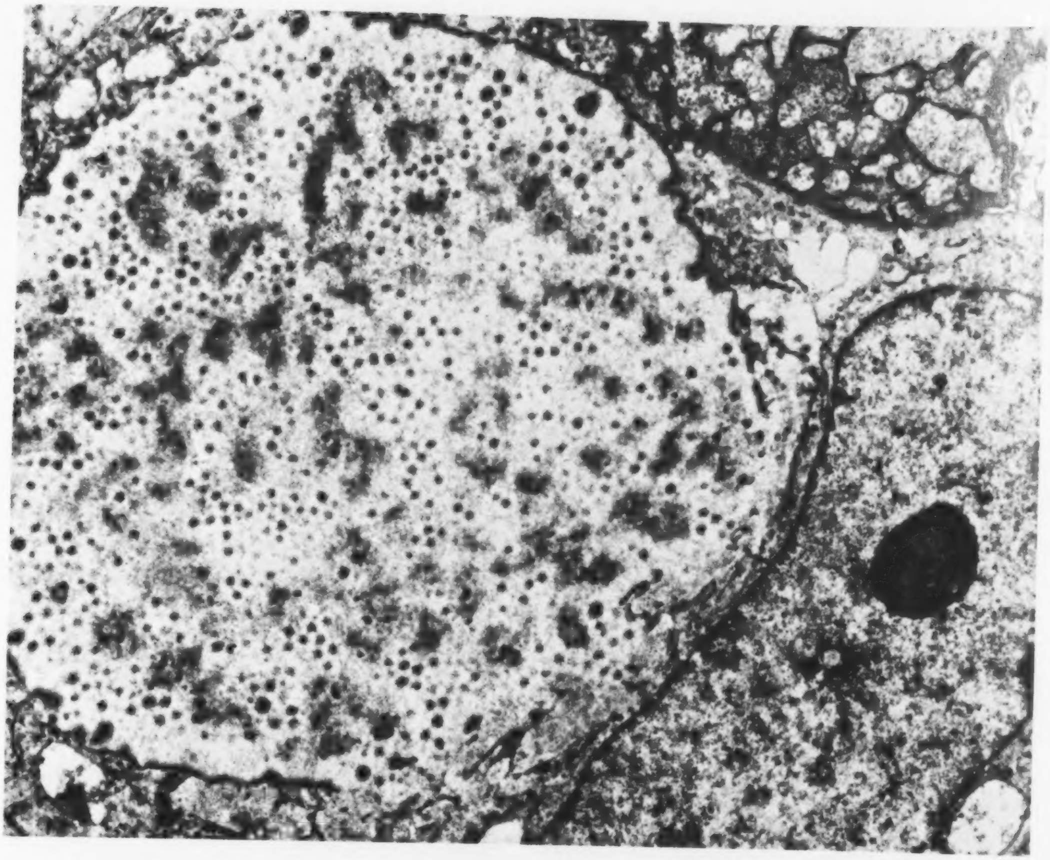

Figure 98
ULTRASTRUCTURE – SIGNET RING CELL ADENOCARCINOMA
A large intracytoplasmic lumen containing mucus has compressed the nucleus (lower right) and cytoplasmic structures. X8990.

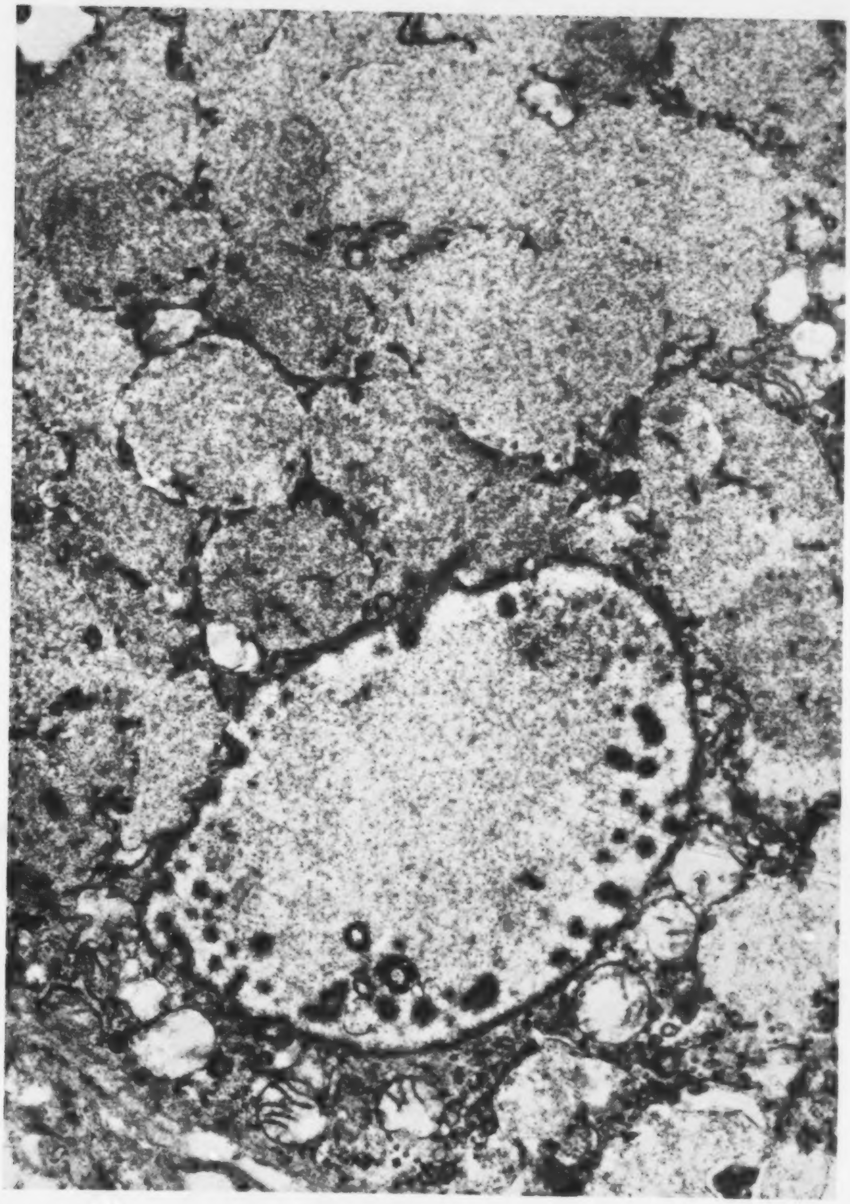

Figure 99
ULTRASTRUCTURE – SIGNET RING CELL ADENOCARCINOMA
A small intracytoplasmic lumen containing microvilli and mucus is visible. In the rest of the cytoplasm, there is abundant mucus material and scattered mitochondria. X14,400.

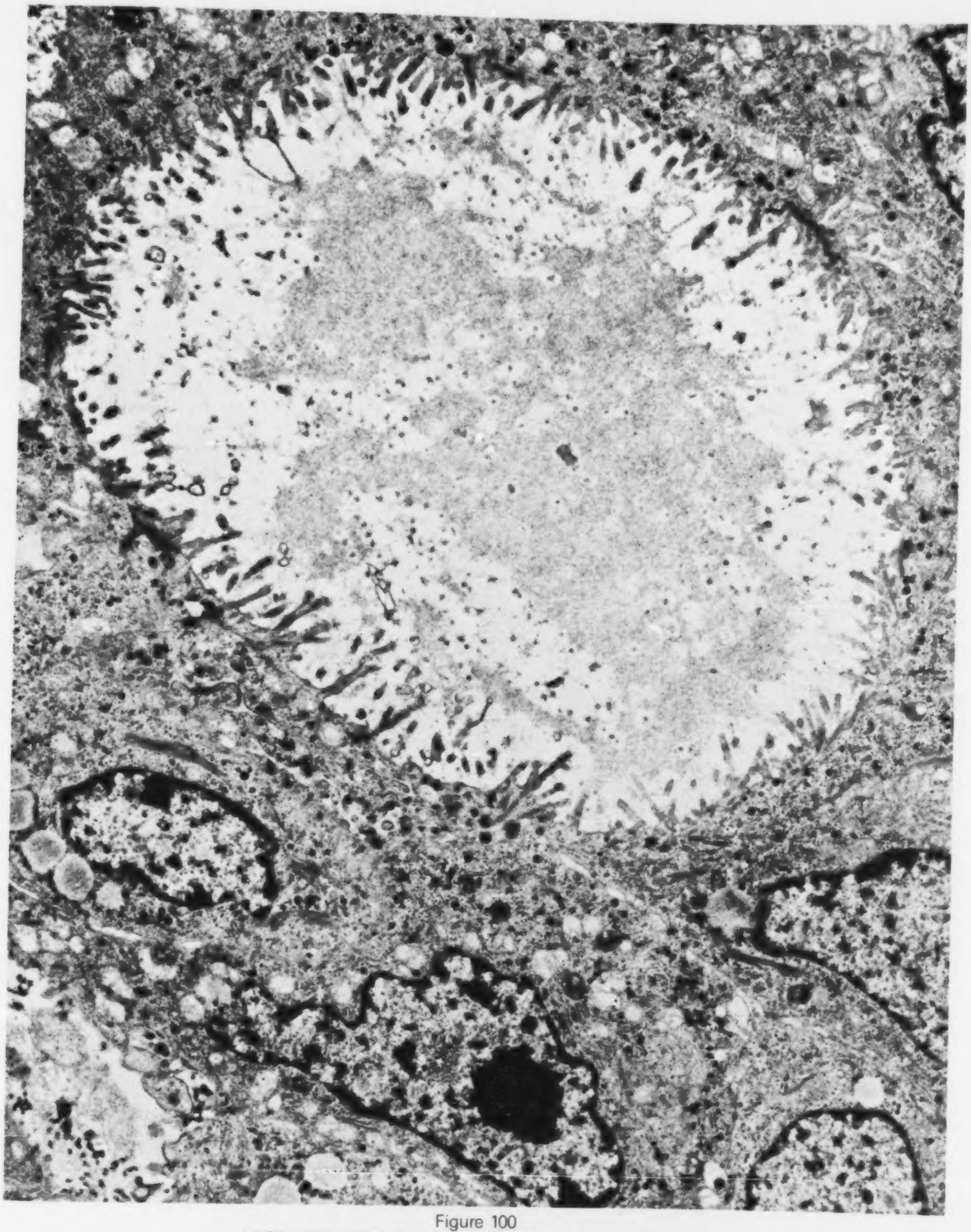

Figure 100
ULTRASTRUCTURE – ADENOSQUAMOUS CARCINOMA
A glandular structure contains mucus and is lined by epithelial cells with long microvilli, one of which exhibits dense core rootlets. In addition to mucin, the cytoplasm of the neoplastic cells contains tonofilament bundles. This dual cellular differentiation is a characteristic feature of adenosquamous carcinomas. Uranyl acetate and lead citrate. X10,545.

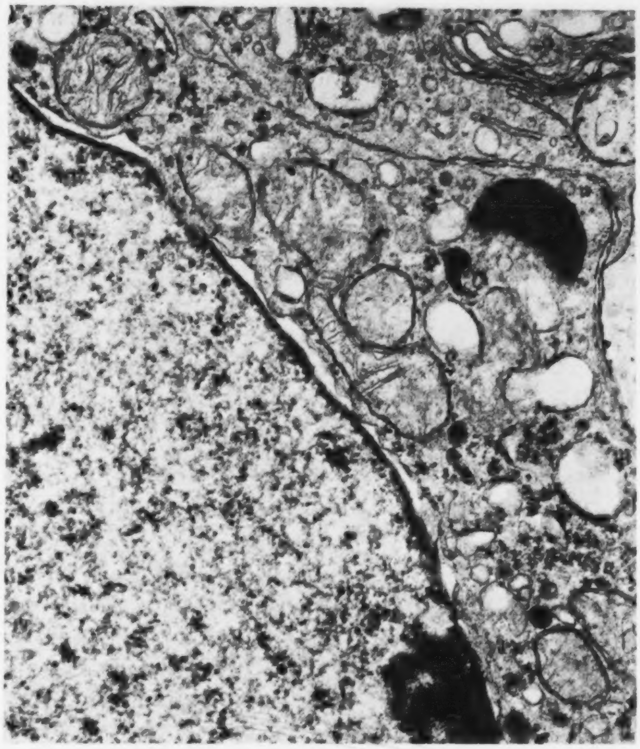

Figure 101
ULTRASTRUCTURE — OAT CELL CARCINOMA
Portions of two cells, one of which contains three small membrane-bound neurosecretory granules. Uranyl acetate and lead citrate. X25,710. (Courtesy of Dr. J. Rosai, Minneapolis, MN.)

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SPREAD

Malignant tumors of the gallbladder are insidious in their spread, often metastasizing early before a diagnosis is made. As a result of the location of the gallbladder, these tumors can spread by several routes – direct extension, through lymphatic and vascular channels, transcoelomically, and along small nerves.

By contiguous growth, tumors can extend into adjacent liver; or invade the stomach, duodenum, or colon; or implant on peritoneal surfaces. Invasion of an adjacent viscus frequently leads to a biliary-enteric fistula, the clinical manifestations of which may be the first indication of cancer. Viable fragments may break away from the main tumor mass, after it has penetrated the wall of the gallbladder, and implant in the pelvic area or on other peritoneal surfaces, leading eventually to intra-abdominal carcinomatosis. Carcinomas of the gallbladder can give rise to Krukenberg tumors of the ovary (figs. 102, 103). In our series, 6 percent of patients had Krukenberg tumors, most of whom also had peritoneal metastases. In the late nonresectable stages of the disease, there may be widespread intra-abdominal metastases and ascites.

A serious complication associated with high mortality and morbidity is perforation of the gallbladder with resultant peritonitis, pericholecystic abscess, or fistula (Kotorac). There are many reports of patients who died from peritonitis and who were found at autopsy to have an acutely perforated carcinomatous gallbladder. Most patients with perforated gallbladders, however, follow a chronic course, with abscess formation or fistula to the colon or duodenum.

Metastases to regional lymph nodes, especially those along the cystic duct and porta hepatis, can occur early, and are one reason for the bad prognosis. Tumors usually spread, at least initially, to the cystic or pericholedochal lymph nodes and later to the peripancreatic and preaortic nodes. More distant metastases may arise in the mediastinal, tracheobronchial, and supraclavicular nodes. Nodal metastases are present in approximately 50 percent of patients at the time of diagnosis, although this figure varies from 25 percent to 80 percent in different studies.

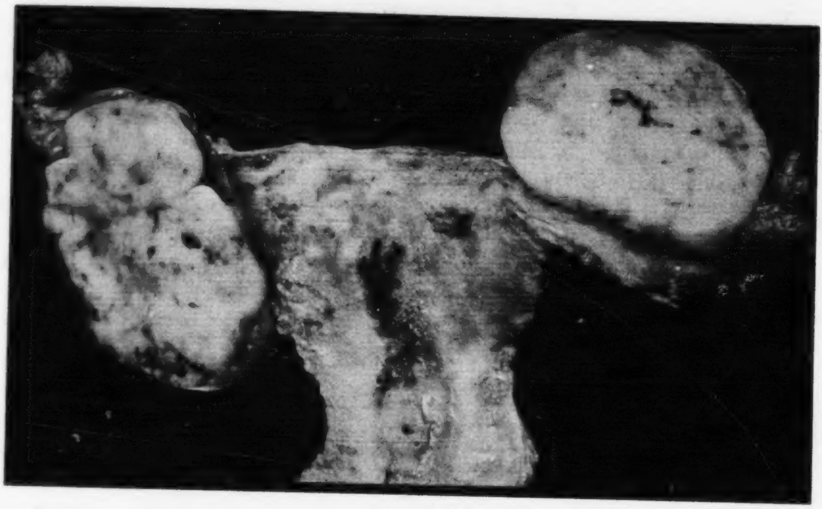

Figure 102
(Figures 102 and 103 from same patient)
KRUKENBERG TUMOR
Ovaries are enlarged, although their overall shape is preserved. Both have been replaced by gray white tumor that originated in the gallbladder.

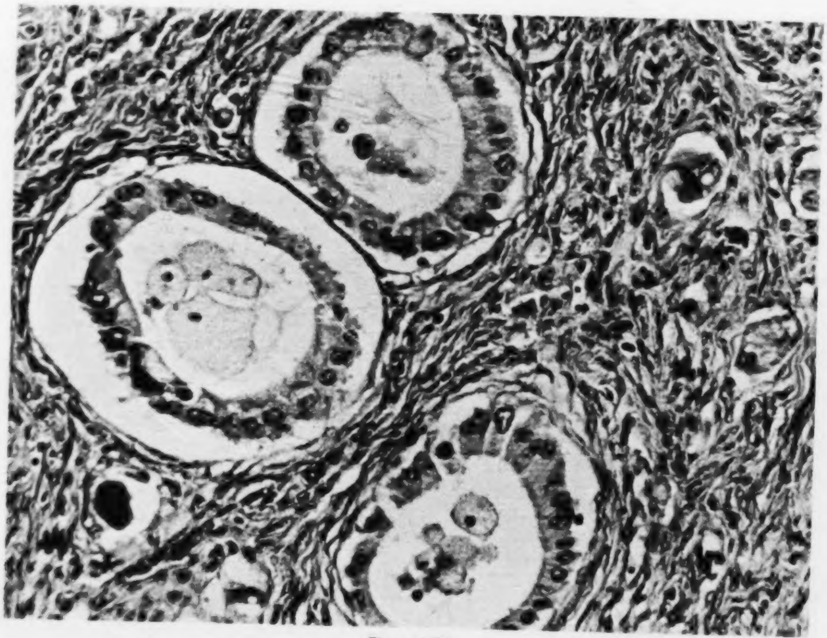

Figure 103
KRUKENBERG TUMOR
Sections from the tumor shown in figure 102. In addition to the well formed neoplastic glands, the stroma appears hyperplastic and contains scattered tumor cells. X200.

Hematogenous dissemination occurs, but, except for the liver and lung, it is unimportant compared to other routes.

Carcinomas of the gallbladder can also invade small nerves (fig. 104). Usually demonstrated microscopically, it is uncertain how important this mode of spread is clinically. It is suspected, however, that neural invasion is a cause of abdominal pain.

By the time of postmortem examination, over 90 percent of patients have metastases in the liver and 80 percent in regional lymph nodes (Perpetuo et al.; Kirshbaum). The lungs, pleura, diaphragm, and peritoneum are other common sites of metastatic spread.

Early Spread

The apparent ease by which gallbladder cancer spreads can be explained from the anatomy. The gallbladder has a thin wall. It has a narrow lamina propria and a single muscle layer. A second muscle layer which would provide another barrier to the centrifugal growth of tumor is not present. Furthermore, extension through the muscle layer brings the tumor into the perimuscular connective tissue, where it has access to major lymphatic and vascular channels.

This proclivity for early spread, before the appearance of signs and symptoms, includes all types of malignant tumors known to occur in the gallbladder with the possible exception of papillary carcinoma.

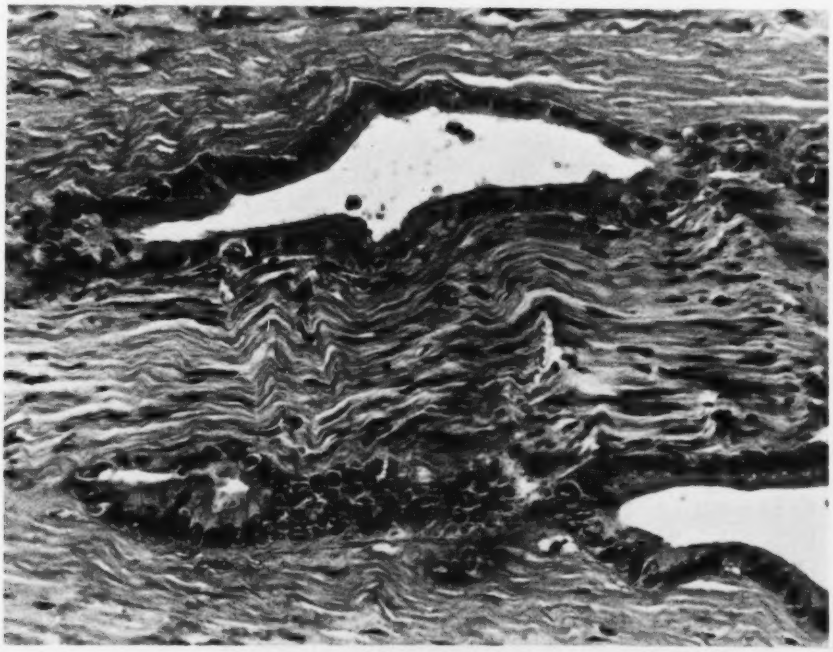

Figure 104
NERVE INVASION
Perineural invasion in a case of well differentiated adenocarcinoma of the gallbladder. X200.

Liver Involvement

Found in 70 percent of patients at the time of surgical evaluation, involvement of the liver usually precludes complete resection of the tumor (fig. 105; pl. III-A). Not only does proximity to the liver favor early and direct extension, but tumor can invade via two other routes — vascular and lymphatic. Of these three routes, direct extension is most common followed by retrograde lymphatic spread (Fahim et al.). A localized mass in the liver in the region of the gallbladder fossa is considered evidence for direct invasion. Owing to obstruction of the biliary tract by tumor, other intrahepatic lesions such as cholestasis and cholangitis can occur (pl. III-B).

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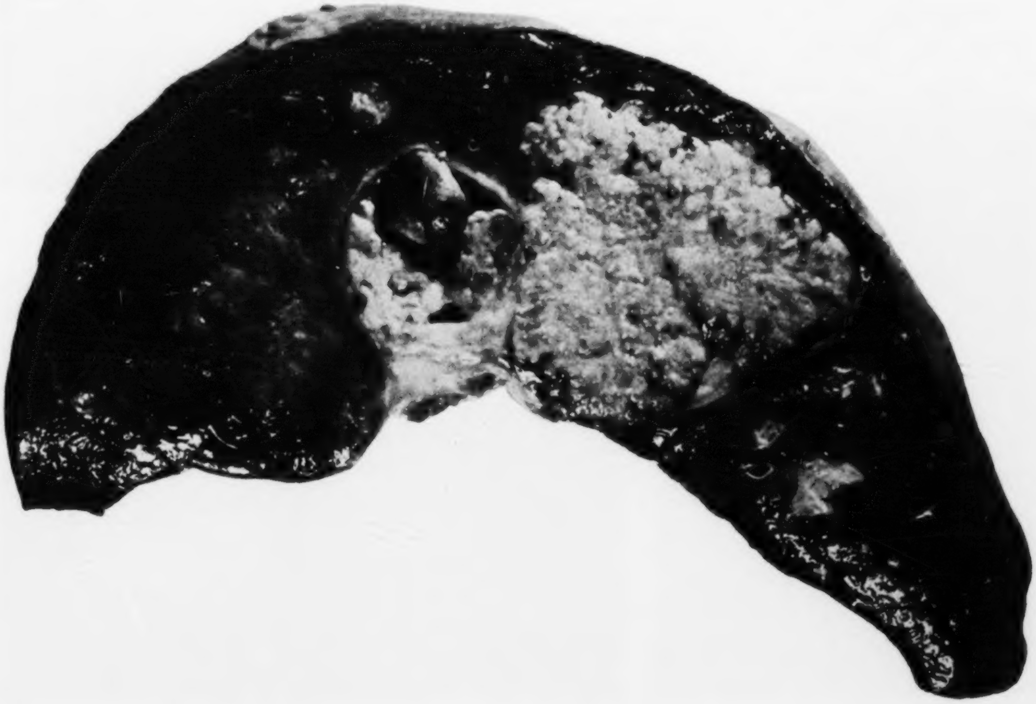


Figure 105
INVASION OF THE LIVER
Direct extension from the gallbladder into the liver. This is the most common type of spread of gallbladder carcinoma.

PLATE III

A. ADENOSQUAMOUS CARCINOMA

This adenosquamous carcinoma extended into the liver. In order to excise the tumor, a cholecystectomy and a right hepatic lobectomy were performed.

B. CHOLANGITIC ABSCESSES

An adenocarcinoma of the gallbladder had been previously excised from the patient. The tumor recurred and invaded the extrahepatic bile ducts, leading to obstruction and ascending cholangitis.

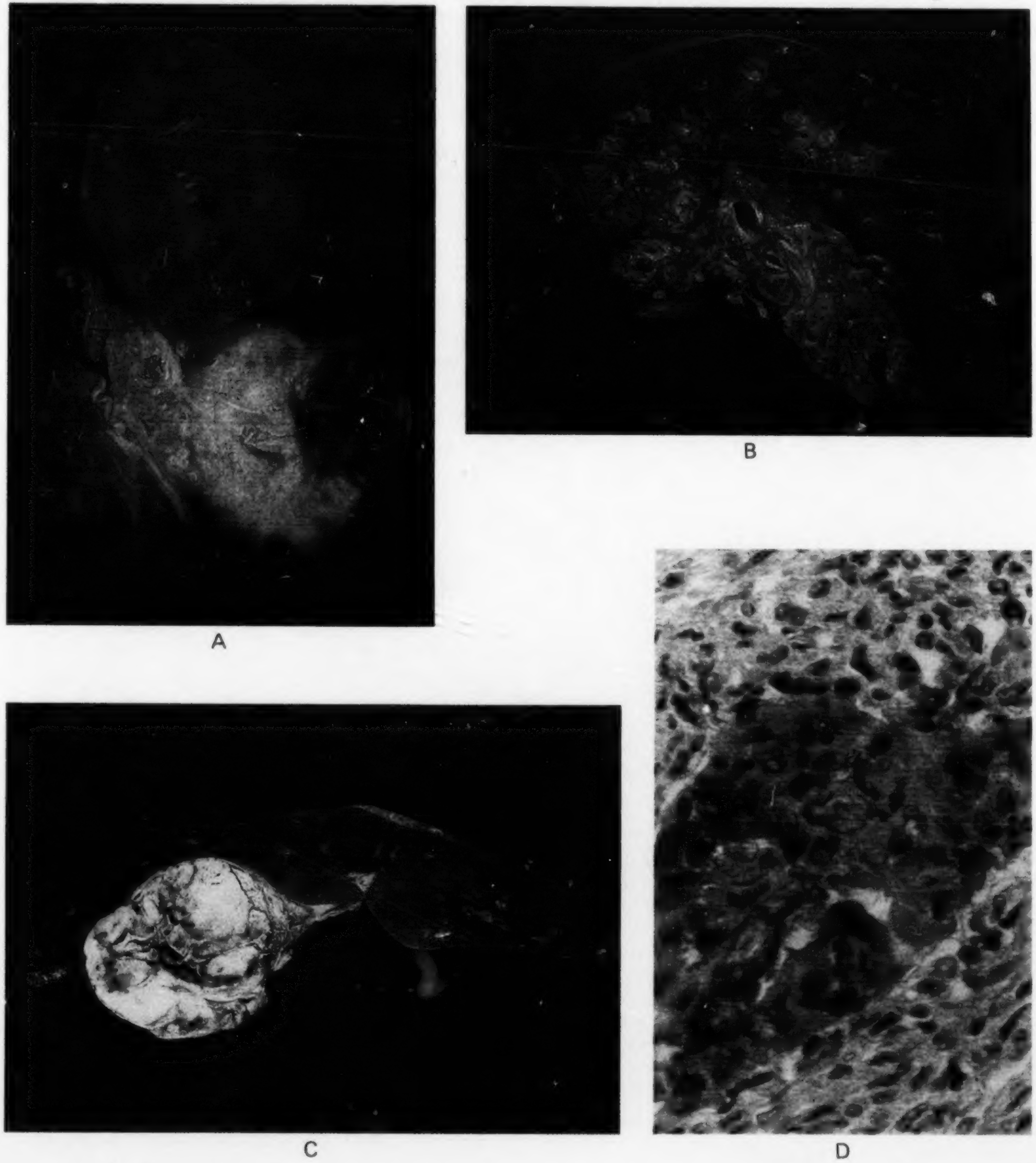
C. CARCINOSARCOMA

The tumor was large, partially necrotic, and filled the entire lumen, distending the gallbladder. However, it did not invade the liver nor metastsize.

D. CARCINOSARCOMA

CEA is present in the squamous component, but not in the stroma. PAP. X125.

PLATE III



A

B

C

D

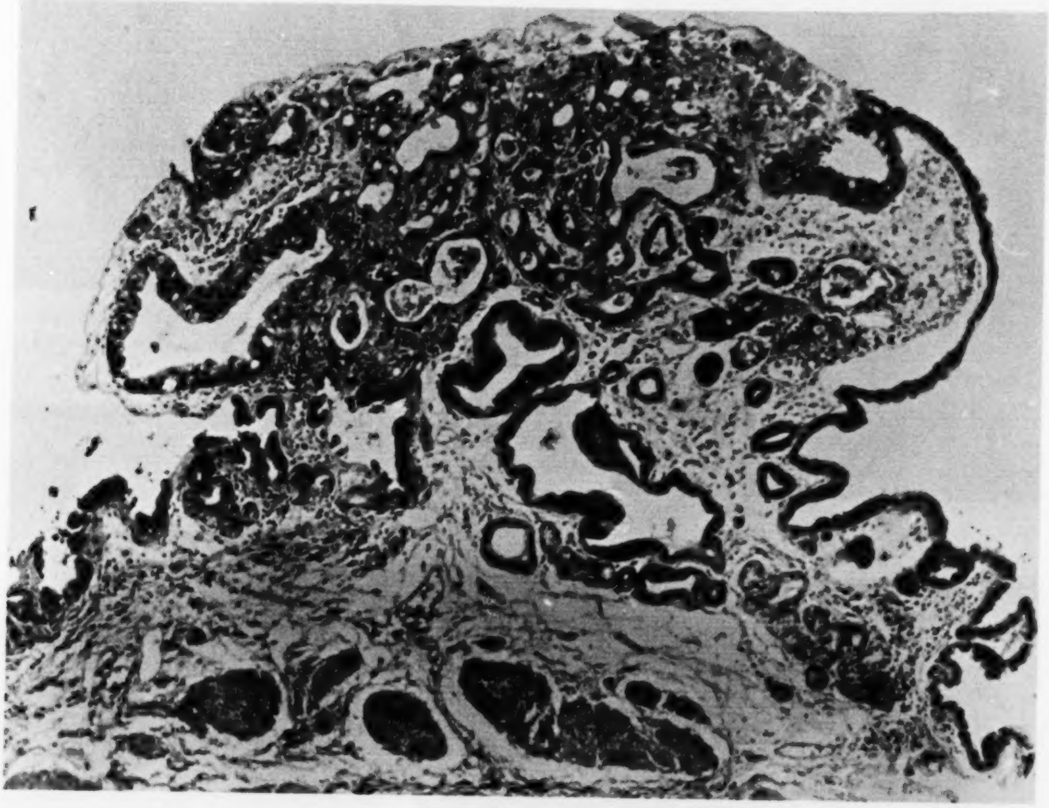


Figure 106

INVASION LIMITED TO LAMINA PROPRIA

A small polypoid infiltrating adenocarcinoma is shown. The infiltrating glands have extended only to the lamina propria. The patient was initially discovered to have an in situ carcinoma, which led to additional sections that revealed this tumor. Invasion into the lamina propria is pathologic Stage T1. X35.

Staging

Because gallbladder cancer is relatively uncommon and usually diagnosed late, pathologists have tended to ignore pathologic staging, even though its importance for survival, management, and prognosis has been stressed (Bivins et al.; Nevin et al.; Bergdahl).

Based on the structure of the gallbladder and the extent of spread, carcinoma of the gallbladder can be divided into a number of stages. For our material we adopted the following, which is consistent with the TNM system promulgated by the American Joint Committee on Cancer (Beahrs and Myers):

T_{is} In situ carcinoma

T1 Invasion limited to the lamina propria or to the muscle layer (figs. 106, 107)

T2 Invasion limited to perimuscular connective tissue. No extension beyond serosa or into liver

T3 Involvement of all layers and direct extension beyond serosa into one adjacent organ, or both (must be less than 2 cm into the liver)

T4 Involvement of all layers and direct extension 2 cm or more into liver or into two or more adjacent organs including: stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts, and any involvement of liver

There is one limitation to this staging procedure. Occasionally, the gallbladder wall may appear completely replaced by fibrous tissue and the normal layers no longer visible. In these cases, measurement of the depth of invasion can be useful. There have been other attempts to classify gallbladder cancer according to the TNM system (Brgadze and Shapkin).

In our review of 386 patients with gallbladder cancer, the pathological stage correlated with survival. Other investigators using comparable staging systems have found a similar correlation between stage and survival (Nevin et al.; Chart 1). Pathological staging is the most convenient and useful way to estimate prognosis, and we strongly endorse its use.

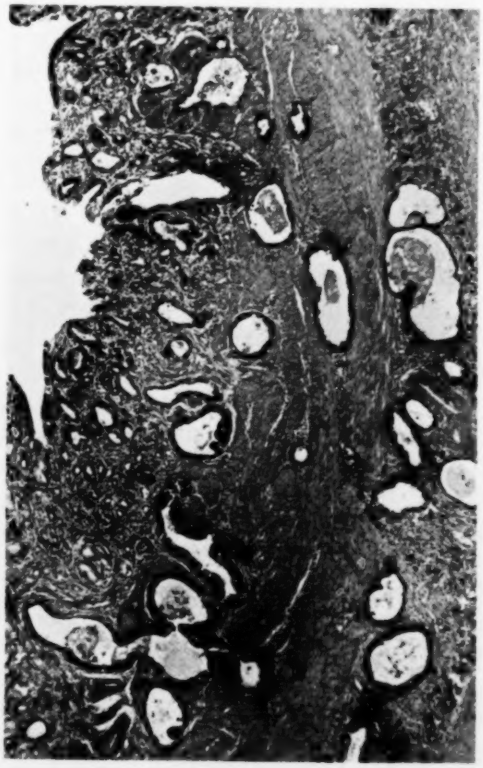


Figure 107
INVASION OF THE
PERIMUSCULAR CONNECTIVE TISSUE
A well differentiated adenocarcinoma has invaded the muscle layer and perimuscular connective tissue. X35.

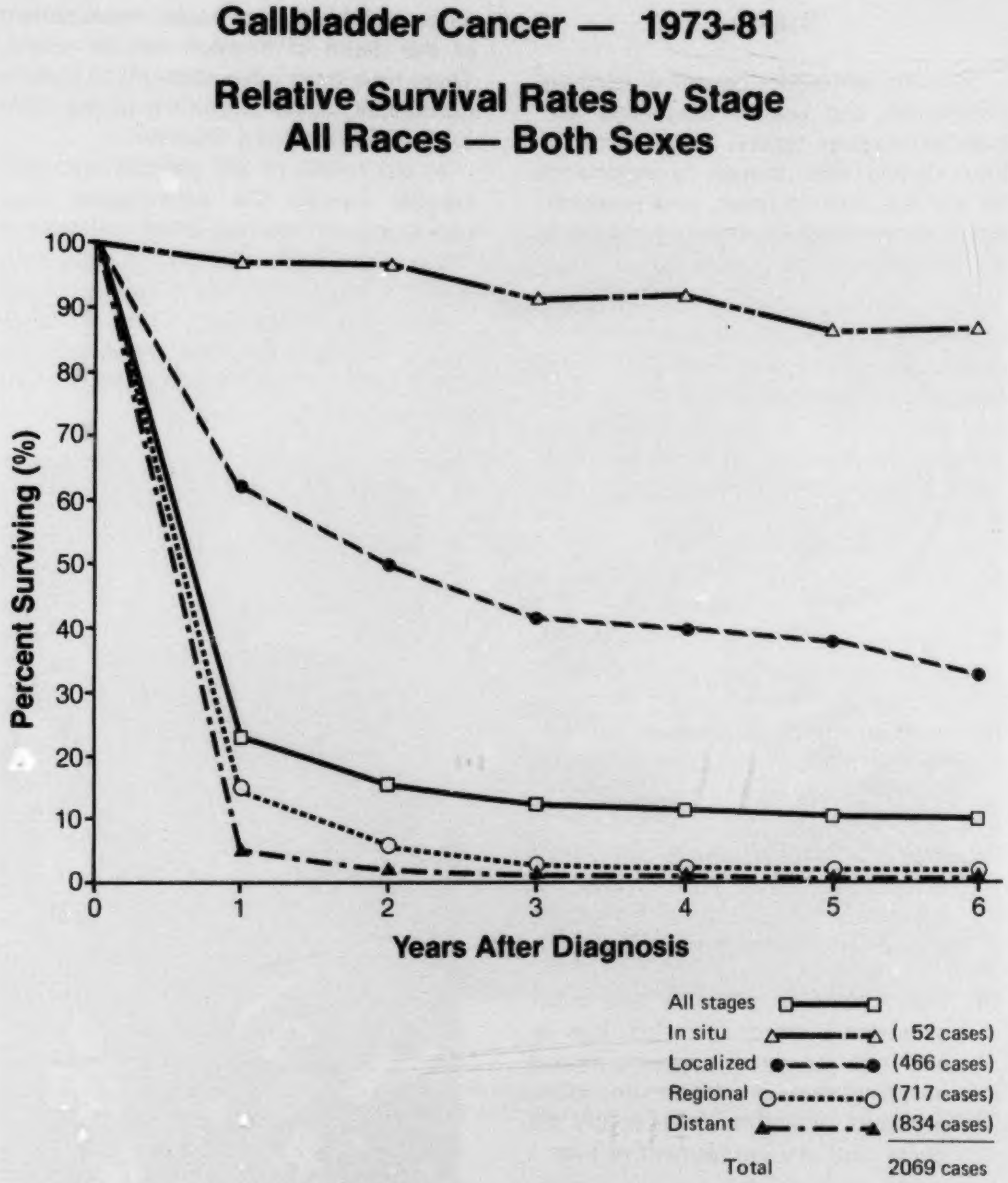


CHART 1

Comparison of the relative survival of patients with gallbladder cancer and the stage of the tumor at time of diagnosis. Data and staging system from Surveillance, Epidemiology and End Results Program, National Cancer Institute.

Prognosis

All surgeons are familiar with the poor prognosis of gallbladder cancer. In fact, survival is no better now than it was 85 years ago (Ames). The single most important factor having the greatest effect on survival is the extent of tumor at the time of diagnosis. For those patients with known metastases at the time of surgery, the median survival is 5.2 months (Perpetuo et al.). For patients without visible metastases, the mean survival is three years (Richard and Cantin). In a collective review, the five-year survival of 1,061 patients was 1 percent (Strauch). In general, five-year survival rates have averaged around 5 percent.

However, as expected from a consideration of other sites, survival is related to the pathologic stage of the disease (Vadheim et al.; Bivins et al.; Bergdahl). Patients with stage T_{is}, or in situ carcinoma, are cured by cholecystectomy. Patients with stage T1, that is, tumor invasion limited to the lamina propria or muscle coat, have a high survival, whereas those with stage T3 or T4 can expect a short survival, usually measured in months.

A correlation between histologic grading and survival was shown by some authors, but this relationship has not been confirmed by others (Wanebo et al.).

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CARCINOSARCOMA

SYNONYMS AND RELATED TERMS: Malignant mixed tumor.

This tumor is composed of both a sarcomatous stroma and carcinomatous elements which include glands and squamous cells. The glandular or squamous component may be prominent and easily recognized, or it may be subtle and difficult to discern under low power of the microscope (figs. 108–110). The malignant stroma contains predominantly spindle cells with elongated nuclei and eosinophilic cytoplasm. These spindle cells resemble fibroblasts and are usually arranged in broad interlacing bundles. Some bizarre multinucleated giant cells having hyperchromatic nuclei may also be present. A storiform pattern may be evident in some areas. Numerous mitotic figures, some abnormal, are readily identified in the stromal cells. Between these cellular elements there are many collagen and reticulin fibers, a feature which serves to distinguish this lesion from a pleomorphic giant cell carcinoma. Some carcinosarcomas may

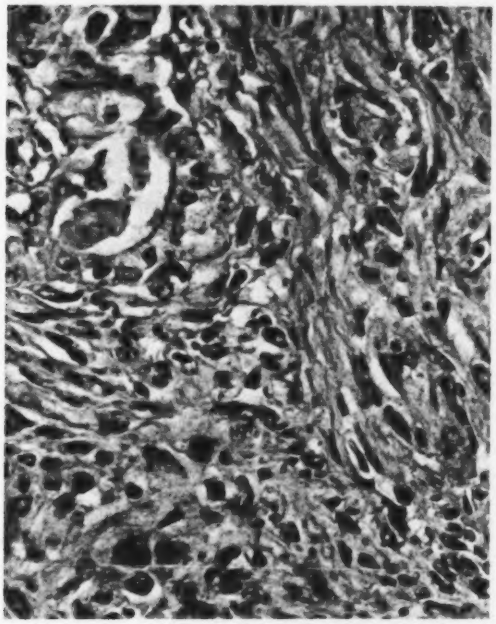

Figure 108
CARCINOSARCOMA
A well differentiated neoplastic gland is surrounded by a sarcomatous stroma. X250.

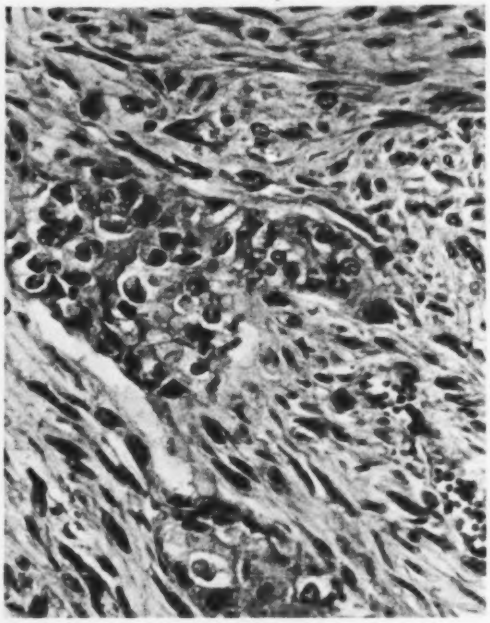

Figure 109
CARCINOSARCOMA
Poorly defined glands are encompassed by bundles of malignant spindle cells. X250.

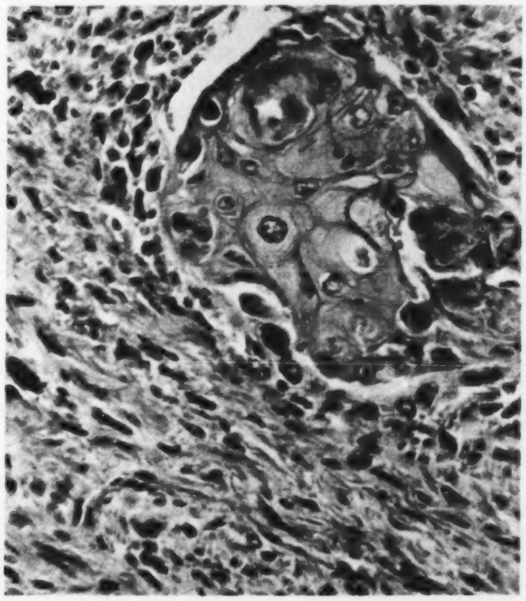

Figure 110
CARCINOSARCOMA
A small focus of well differentiated squamous cells is seen in a sarcomatous stroma. X250.

also contain malignant cartilage and bone (figs. 111, 112; Higgs et al.; Mansori and Cho; Mehrotra et al; von Kuster and Cohen).

Grossly, carcinosarcomas are large polypoid tumors that can measure from 6 cm to 15 cm and fill most of the gallbladder lumen (pl. III-C). They may be pedunculated or sessile. The cut surface shows gray white or yellow tissue usually with extensive necrosis and hemorrhage. Cartilage can often be recognized as small blue white glistening nodules.

Analysis of the few reported cases and those we have examined personally indicates that the potential to metastasize varies according to the histologic components. It is our impression that tumors containing heterologous tissues, such as cartilage and bone, rapidly invade the wall and extend to adjacent organs, whereas those having only homologous elements tend to be less aggressive and have a better prognosis. A similar divergence in biologic behavior has also been observed with malignant mixed tumors of the uterus.

As a group, these tumors are heterogeneous. In some carcinosarcomas the glandular or squamous component may be quite prominent while in others the stroma predominantes. Classification of those

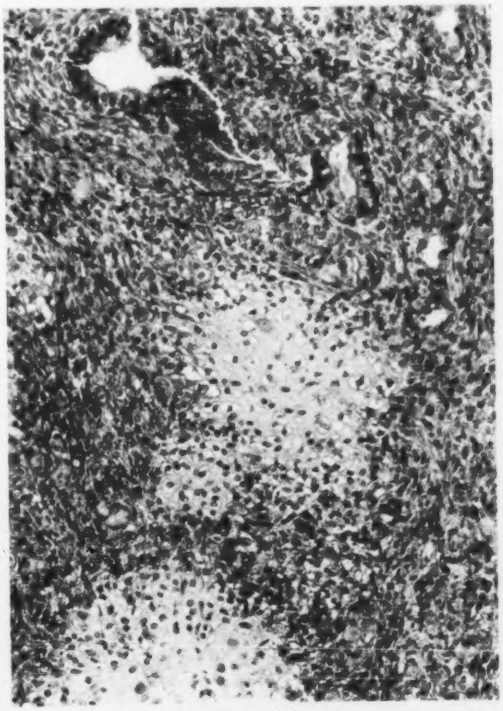

Figure 111
(Figures 111 and 112 from same patient)
CARCINOSARCOMA WITH CARTILAGE
Several foci of malignant cartilage and two neoplastic glands lie in a sarcomatous stroma. X130. (Courtesy of Dr. J.C. Mandard, Caen, France.)

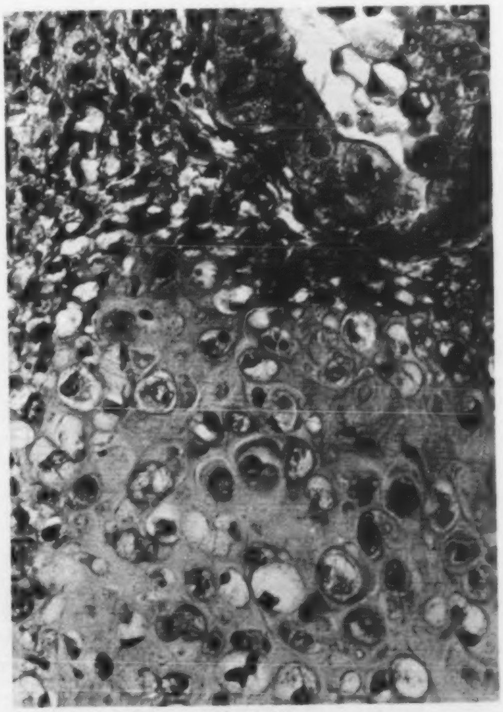

Figure 112
CARCINOSARCOMA WITH CARTILAGE
Higher magnification of the tumor shown in figure 111. The chondrocytes show malignant changes similar to those usually seen in chondrosarcomas. A mitotic figure is present in the gland. X300. (Courtesy of Dr. J.C. Mandard, Caen, France.)

tumors that contain a large proportion of glands or squamous cells may be difficult, but a malignant spindle cell stroma, especially in which there is cartilage or bone, should alert the pathologist to the proper diagnosis (figs. 111, 112).

The origin of the stroma is uncertain, but the fact that CEA is present only in the glandular and squamous components suggests that the spindle cells might be of mesenchymal origin (pl. III-D). Furthermore, keratin can be detected in the squamous cells, but not in the stroma (fig. 113).

These tumors are found in the same age groups as carcinomas of the gallbladder and are usually associated with stones.

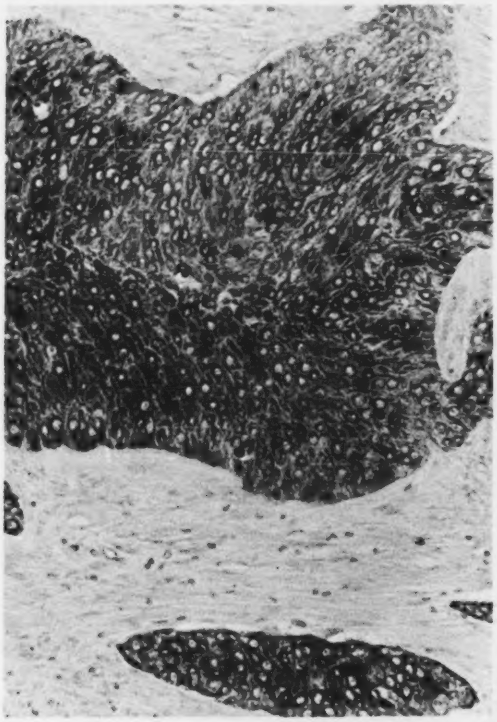

Figure 113
CARCINOSARCOMA
The squamous cell component is positive for keratin, while the stroma is negative. PAP keratin antibody. X100. (Courtesy of Dr. H. Battifora, Duarte, CA.)

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CARCINOID TUMOR

Through 1981, 17 cases of primary carcinoid tumor of the gallbladder had been recorded (Bosl et al.; Vitaux et al.). In at least four patients, the tumor had metastasized. In addition to the 17 cases, three other patients, two of whom developed the carcinoid syndrome, had multiple primary tumors occurring simultaneously in the gallbladder and small intestine with metastases to the mesenteric lymph nodes, heart, bone, and other sites. Carcinoid tumors of the gallbladder represent less than 1 percent of all digestive tract carcinoids.

Grossly, these tumors are usually small gray white or yellow submucosal nodules that may be located in any part of the gallbladder. Histologic sections show small nests of compact cells often in a trabecular arrangement and separated by thin bands of connective tissue (fig. 114). The cells are small and uniform with round nuclei and a slightly granular eosinophilic cytoplasm. In some cases, secretory granules can be demonstrated with silver stains. Carcinoids of the gallbladder should be considered

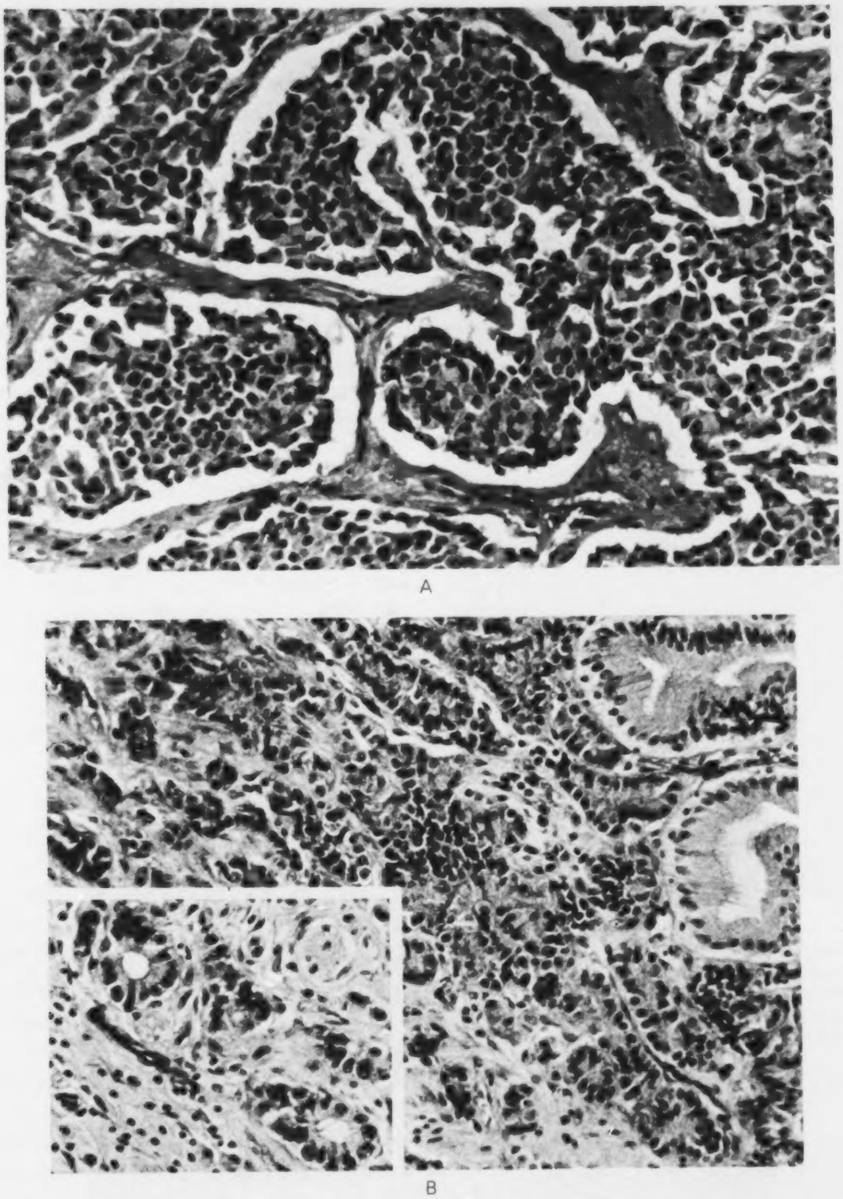

Figure 114
CARCINOID TUMORS OF GALLBLADDER

(A) Nests of small compact cells with an eosinophilic cytoplasm and round nuclei are separated by thin bands of connective tissue. X180. (B) Adenocarcinoid composed of small tubules and cords separated by fibrous connective tissue is growing beneath the gallbladder epithelium. These lesions have been mistaken for adenocarcinomas. X220. Inset shows tubular structures in cross section. X272.

malignant, since in a number of cases the tumor has metastasized. In our view, some carcinoid tumors that disseminate (Bosl et al.) are less differentiated and should be regarded as atypical carcinoids or as oat cell carcinomas.

Carcinoids with a tubular pattern, similar to those found in the appendix (Warkel et al.; Rodriguez et al.), can also occur in the gallbladder (fig. 114). These tumors, which have been called adenocarcinoids, are composed of small tubular structures lined by cuboidal or columnar cells with basal nuclei and an eosinophilic cytoplasm. Many of the lining cells contain argyrophil or argentaffin granules usually, in a subnuclear location. The lumens of the tubules often have mucin which may also be seen in the cytoplasm of the lining cells. These tumors can be mistaken for a well differentiated adenocarcinoma.

Composite tumors of the gallbladder which exhibit both carcinoid and carcinomatous patterns have been reported (Wisniewski and Toker; Wada et al.). We also have seen an atypical carcinoid of the gallbladder, which is discussed under "Oat Cell Carcinomas."

Carcinoid tumors are not limited to the gallbladder, but occur in all parts of the extrahepatic biliary tree including the ampulla (Bergdahl; McRae and Conn; fig. 115). Those that arise in the hepatic or common bile ducts can be a source of obstructive jaundice (Gerlock and Muhletaler; Vitaux et al.).

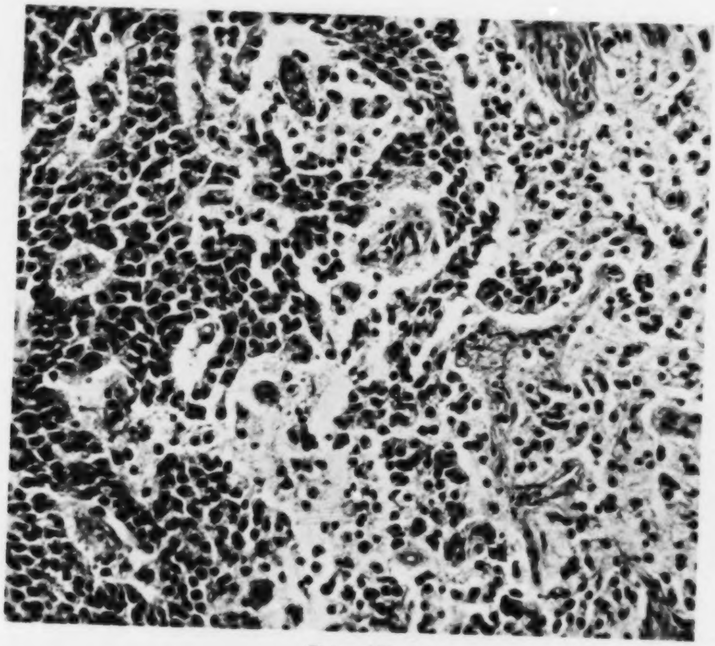

Figure 115

CARCINOID TUMOR OF COMMON BILE DUCT

Anastomosing cords of small hyperchromatic cells are seen in one area, while in the other area the cells are less compact. X250.

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MALIGNANT LYMPHOMA

Malignant lymphomas of any type may infiltrate the gallbladder, although this usually occurs as part of a generalized process (Van Slyck and Schuman).

Primary malignant lymphomas of the gallbladder are exceedingly rare (Botha and Kahn). The only case available for our review was a well differentiated lymphocytic lymphoma that involved the entire thickness of the wall (fig. 116). Despite the neoplastic infiltration, the villous structure of the gallbladder was preserved in some areas. As with lymphomas in other hollow viscera, regional lymph nodes may be involved and dissemination usually occurs later.

Currently, we know of no way to histologically differentiate primary lymphoma from secondary lymphoma in the gallbladder. All lymphomas discovered in cholecystectomy specimens should be presumed secondary and a diagnosis of primary lymphoma made only by careful exclusion (Gillespie et al.).

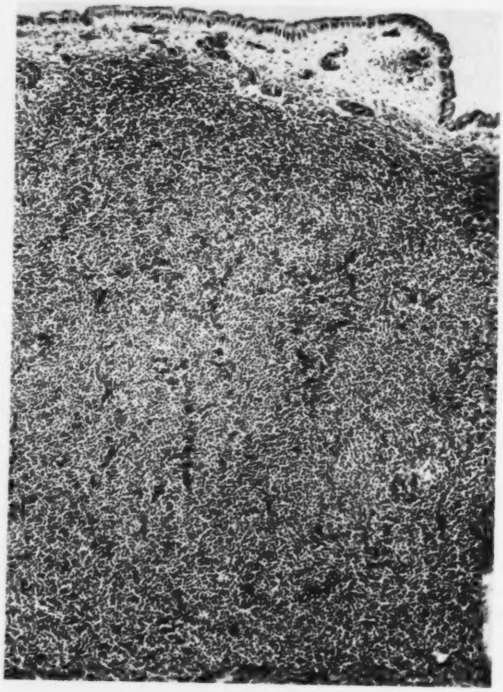

Figure 116
PRIMARY MALIGNANT LYMPHOMA
The wall of the gallbladder is diffusely infiltrated by well differentiated malignant lymphocytes. The epithelium has remained intact, although the mucosal folds are flattened. In other areas, the folds were preserved. X60.

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MALIGNANT MELANOMA

Nearly all malignant melanomas of the gallbladder are metastatic (McFadden et al.). However, several cases have been reported in which no primary tumor was found elsewhere, and the patients either died many years after cholecystectomy from metastatic melanoma or remained well (Walsh; Peison and Rabin). These primary malignant melanomas are usually large, bulky polypoid masses that may show junctional activity along the epithelium overlying the tumor (figs. 117, 118). This junctional activity is diagnostic for a primary melanoma in the gallbladder, although an expanding tumor may have obliterated all junctional changes by the time of histologic examination.

Histologically, these tumors are similar to the more common cutaneous melanomas (Laitio; Carle et al.). Electron microscopic studies in one case revealed melanosomes in tumor cells as well as in normal adjacent epithelium (Hatae et al.). Melanocytes, which are the origin of melanomas, have been observed in the normal human gallbladder (Breathnach). Cases of primary malignant melanoma of the gallbladder should be confirmed by autopsy or long-term followup.

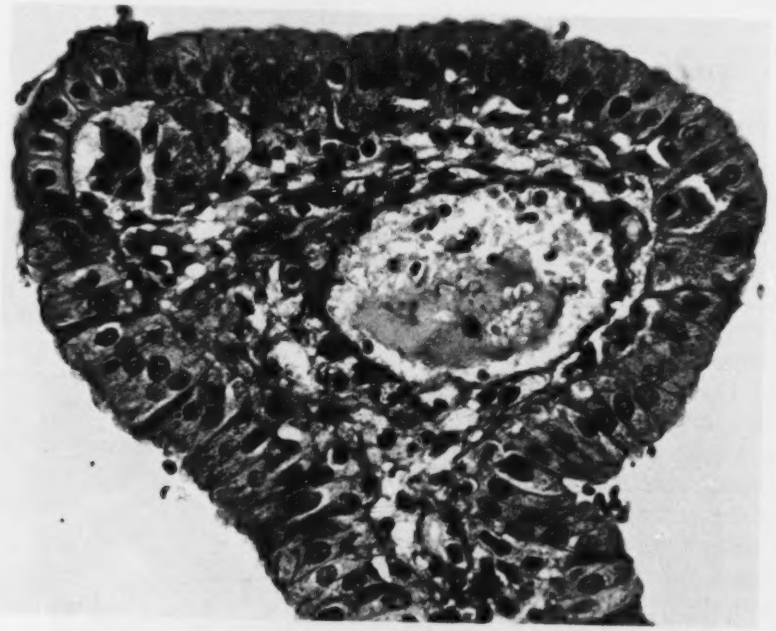

Figure 117
PRIMARY MALIGNANT MELANOMA
Normal gallbladder mucosa showing foci of junctional activity. Note the presence of pigmented melanocytes wedged between the columnar mucosal cells. X310. (From Peison, B. and Rabin, L. Malignant melanoma of the gallbladder. Cancer 37:2448-2454, 1976.)

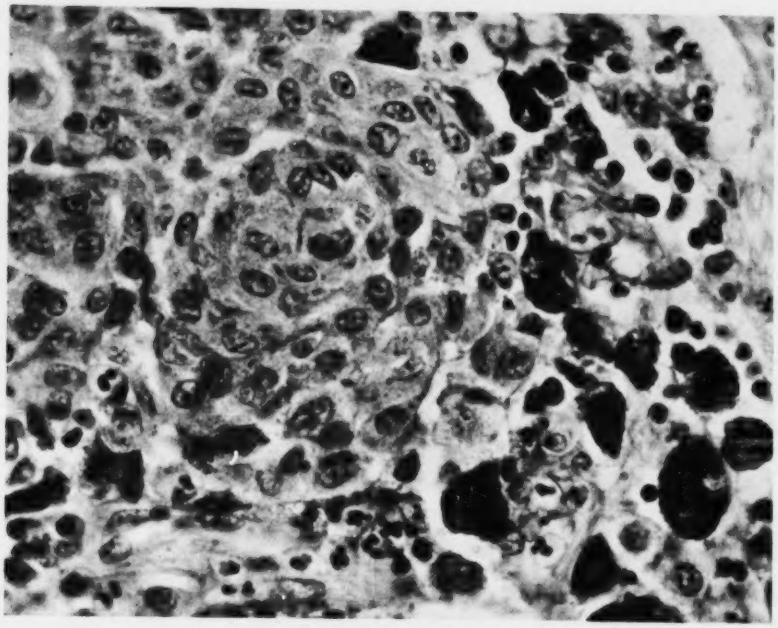

Figure 118
PRIMARY MALIGNANT MELANOMA
Malignant melanoma showing nuclear hyperchromasia and cytoplasmic melanin granules. X440. (From Peison, B. and Rabin, L. Malignant melanoma of the gallbladder. Cancer 37:2448-2454, 1976.)

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MALIGNANT MESENCHYMAL TUMORS

Malignant mesenchymal tumors of the gallbladder are so rare as to constitute medical curiosities (Vaittinen; Willen and Willen). Many of these tumors reported in the older literature, especially those in which no specific cell type was recognized or which were considered spindle, pleomorphic, or round cell sarcomas, were probably pleomorphic giant cell carcinomas or the spindle cell variant of squamous carcinomas. As emphasized by others (Edmondson; Appelman and Coopersmith), pleomorphic giant cell carcinomas can be mistaken for sarcomas.

We have personally studied a rhabdomyosarcoma, a malignant fibrous histiocytoma, and an angiosarcoma of the gallbladder.

The rhabdomyosarcoma occurred in a two year old girl, was of embryonal type, had typical botryoid features, and invaded the liver by direct extension (figs. 119–121). Immunohistologic stains revealed that many neoplastic cells, especially those with an abundant eosinophilic cytoplasm, contained myosin and myoglobin, which have also been found in cells from embryonal rhabdomyosarcomas in other sites (pl. IV-A). A rhabdomyosarcoma of the gallbladder was recently reported in a six year old child (Mihara et al.). In all, less than five documented cases of primary rhabdomyosarcoma of the gallbladder have been described.

The malignant fibrous histiocytoma was a gray white necrotic mass that coexisted with lithiasis. It replaced most of the gallbladder from a 60 year old woman. The tumor extended to the liver, but did not metastasize. It was a densely cellular neoplasm composed of histiocytes and fibroblasts arranged in bundles and showing the characteristic storiform pattern (fig. 122). Numerous collagen fibers were seen between the neoplastic cells.

The angiosarcoma appeared as a small hemorrhagic nodule in the body of the gallbladder that was removed from a 62 year old woman because of symptoms of chronic cholecystitis. However, metastatic lesions appeared in the liver and omentum several months after diagnosis. Its histologic features did not differ from those of angiosarcomas in other locations. Angio-

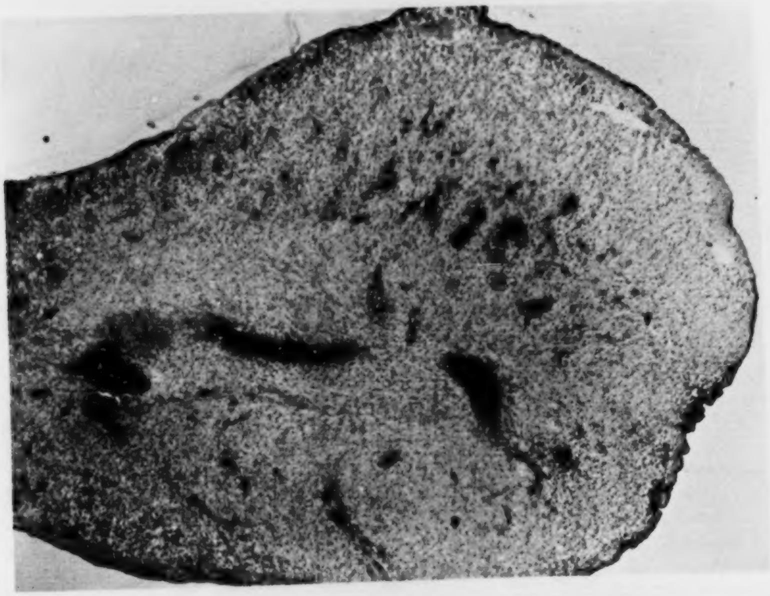

Figure 119

RHABDOMYOSARCOMA

Polypoid structure composed of loose myxoid stroma with many dilated blood vessels. This type of structure is highly characteristic of sarcoma botryoides and should not be mistaken for a benign polyp. X25.

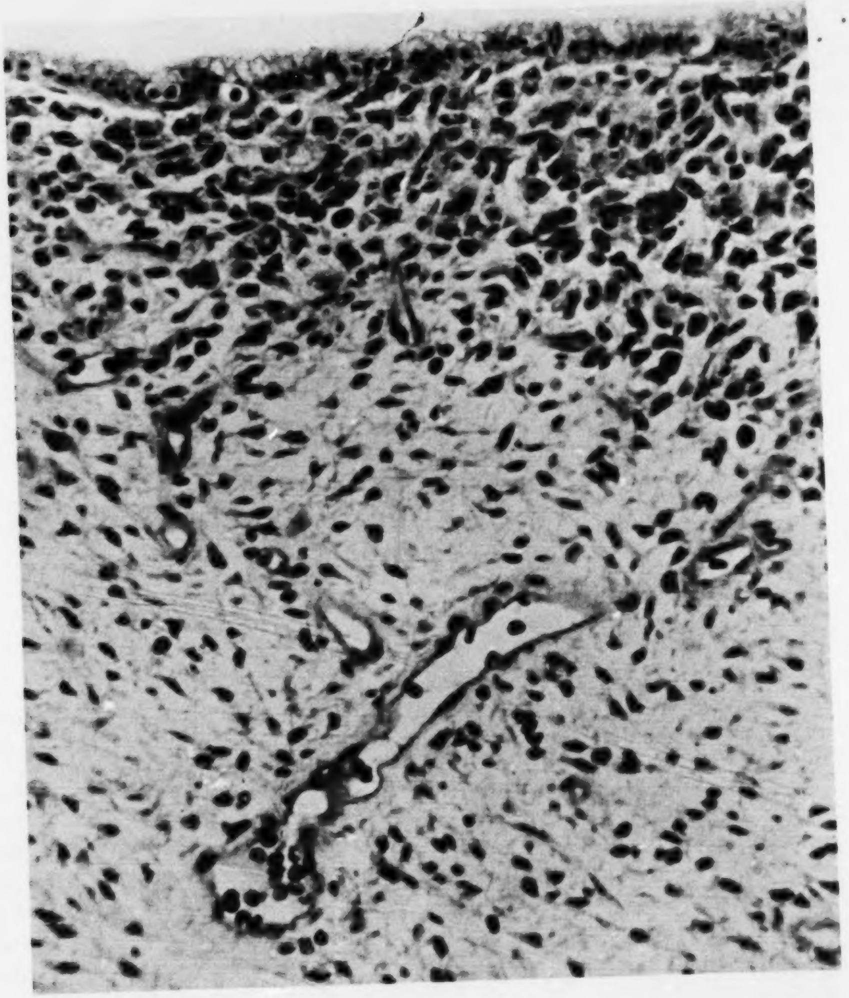

Figure 120
RHABDOMYOSARCOMA
Immediately below the epithelium is a concentration of primitive mesenchymal cells that forms the cambium layer. Myxoid areas are present in the deeper part of the tumor. X250.

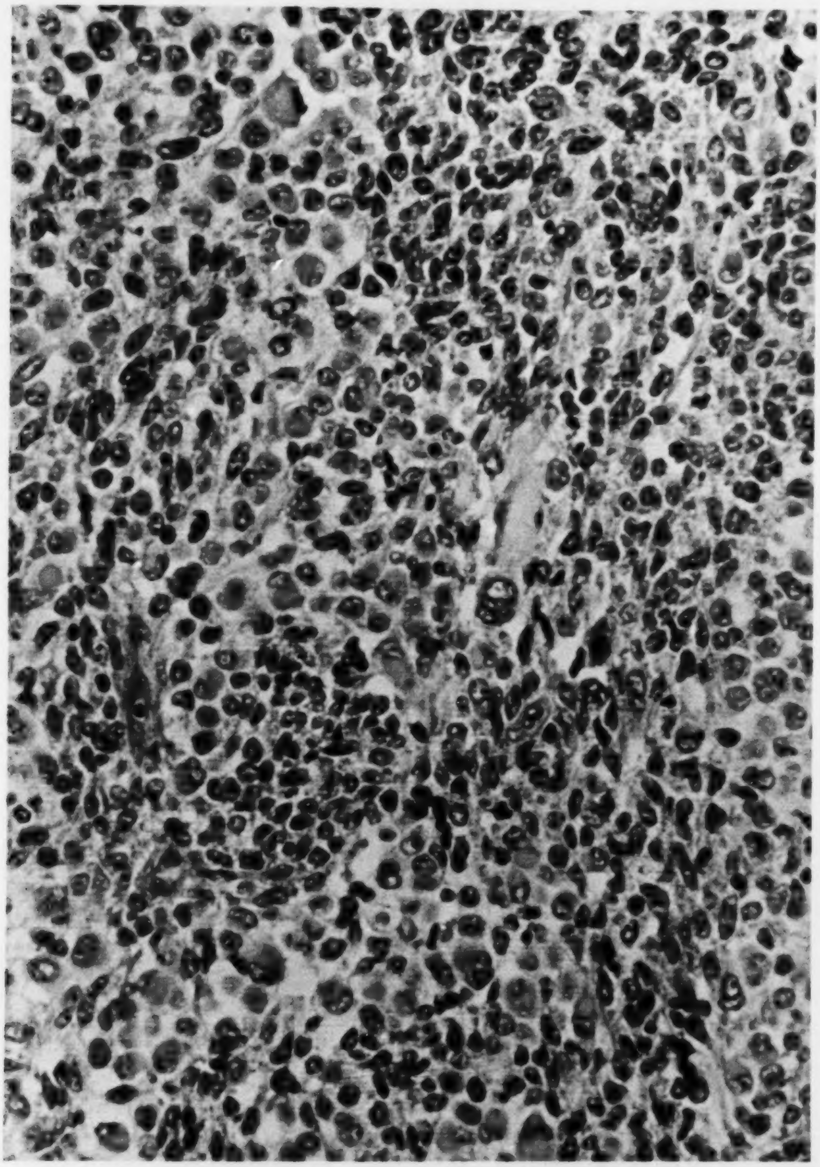

Figure 121
RHABDOMYOSARCOMA
Round and spindle cells are mixed with rhabdomyoblasts which have a globular cytoplasm. X250. (Courtesy of Dr. P. Valencia Mayoral, Mexico City, Mexico.)

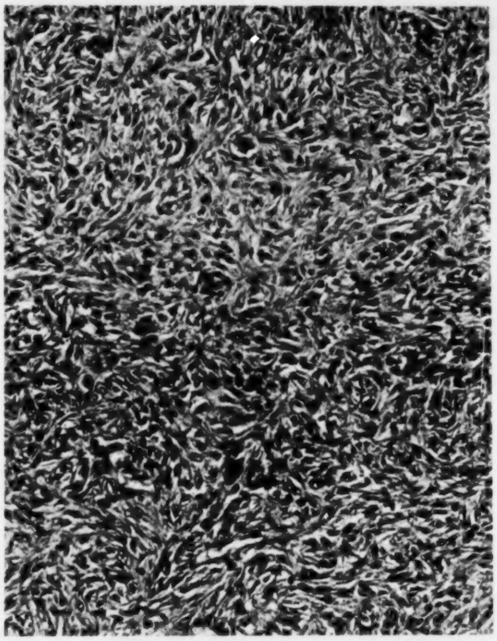

Figure 122
MALIGNANT FIBROUS HISTIOCYTOMA
These spindle cells, which are mixed with histiocytes, are arranged in bundles with areas showing a storiform pattern. X130. (Courtesy of Dr. J. Aguirre, Mexico City, Mexico.)

sarcomas have been seen in the gallbladder by others.

We have also seen involvement of the gallbladder by Kaposi's sarcoma in patients who have died with the Acquired Immunodeficiency Syndrome. The hemorrhagic lesions were located mainly in the perimuscular connective tissue. The extrahepatic bile ducts were also involved in one patient.

A few primary leiomyosarcomas, which probably originated in the muscle layer, have been reported (Schmidt; Willen and Willen). Their histologic structure is similar to that of leiomyosarcomas in other sites, and they can cause the same problems in diagnosis (fig. 123).

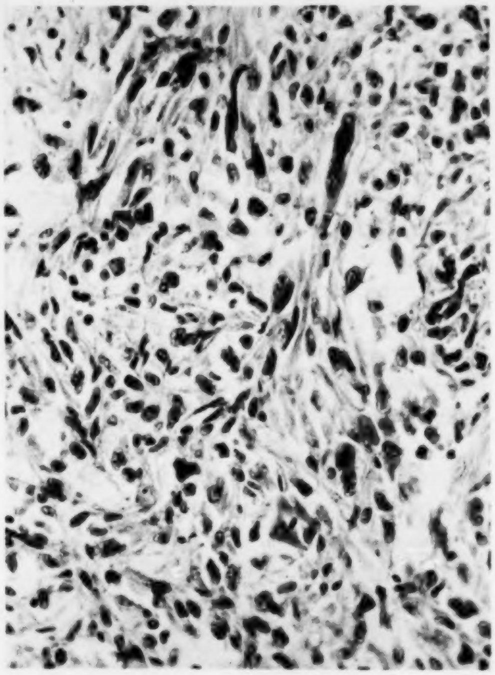

Figure 123
LEIOMYOSARCOMA
Smooth muscle cells are arranged in bundles. Some cells have large hyperchromatic nuclei. X250. (Fig. 71 from Fascicle 26, First Series.)

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BILE CYTOLOGY

Although transhepatic cholangiography, selective angiography, ultrasound examination, and computed tomography (fig. 124) have contributed greatly to the preoperative diagnosis of malignant biliary tract tumors, it seems unlikely that these methods will improve prognosis. In fact, most neoplasms visualized by these procedures have been invasive, relatively large, and often far advanced (Silvis et al.). Radiographic findings, on the other other hand, are not pathognomonic of malignancy, and separation of tumors from inflammatory conditions is occasionally very difficult.

Normal, atypical, and neoplastic cells desquamate into bile, where they can be identified. Therefore, we believe that bile cytology can become an important tool in the preoperative diagnosis of in situ and early invasive carcinomas of the gallbladder and extrahepatic ducts. In fact, bile cytology has certain advantages, especially for the gallbladder, in that a larger representation of the surface epithelium can be sampled than by one or two routine histologic sections. It seems reasonable that common use of preoperative bile cytology in high-risk patients will increase the diag-

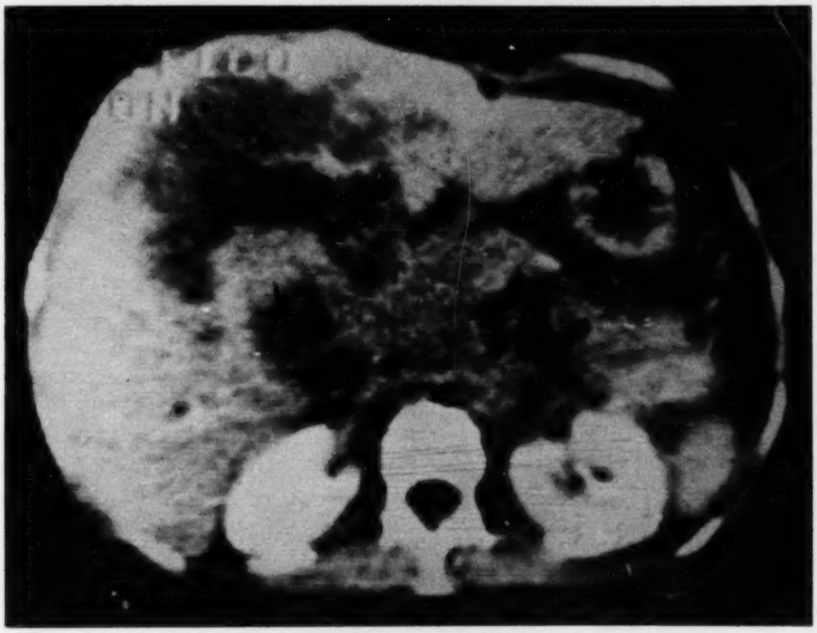

Figure 124
COMPUTED TOMOGRAPHY
Computed tomography showing a vegetating and infiltrating mass (arrow) that was subsequently shown to be an adenocarcinoma in the fundus of the gallbladder. The tumor extended to the right hepatic lobe and to the common bile duct, which is dilated. (Courtesy of Dr. G. Moreno, Mexico City, Mexico.)

nosis of early or small cancers, enabling the surgeon to approach the patient with this knowledge.

Reasons why bile cytology has not been used more widely in the diagnosis of gallbladder or extrahepatic bile duct carcinoma include (1) the inherent technical difficulties of collecting bile directly from the gallbladder or from the bile ducts, and (2) the low incidence of carcinoma of the biliary tree in many geographic areas has provided little incentive or need for the test.

COLLECTION OF BILE

Clinically, bile for cytology can be collected several ways. It can be obtained directly from the common duct by aspiration under direct vision, using different types of duodenal fiberscopes. With this technic, 100 percent of carcinomas of the ampulla, 83 percent of bile duct carcinomas, and 25 percent of carcinomas of the gallbladder were successfully diagnosed (Harada et al.). The combination of endoscopic retrograde cholangiography and cytology increased diagnostic accuracy to 90 percent for bile duct carcinomas and to 50 percent for gallbladder carcinomas.

Bile can also be collected by gallbladder puncture during peritoneoscopic examination. In a series of 110 punctures, only one patient developed peritonitis, which resolved under conservative treatment (Ropertz and Wagner).

Bile can be decanted from the gallbladder immediately after cholecystectomy. Through this simple procedure, pathologists can become familiar with the cytology of dysplasia, carcinoma in situ, and invasive carcinoma of the gallbladder, especially from a study of bile obtained from high-risk patients. To insure good cell preservation and prevent autolysis, bile should be collected and centrifuged and smears prepared immediately following removal of the gallbladder. In our experience, this simple technic has helped to identify dysplasia and carcinomas in situ (Alonso de Ruiz et al.). It has great advantage in those cases in which an invasive carcinoma is not suspected grossly and therefore may easily be missed because of inadequate sampling. If malignant cells are present in the bile smears, but the histologic sections show only inflammatory changes, additional sections must be submitted for diagnostic confirmation.

Bile obtained by aspiration during transhepatic cholangiography has occasionally been reported as useful for the diagnosis of bile duct and gallbladder carcinoma. With this procedure, a correct diagnosis can be made in nearly 80 percent of patients with cancer of the extrahepatic biliary system. If bile from the common bile duct or the duodenum contains malignant cells, clinicopathologic studies are still necessary to locate the tumor, since carcinoma of the gallbladder, bile ducts, intestine, and pancreas are cytologically indistinguishable.

The incidence of false positive results in preoperative bile cytology is less than 1.0 percent. Histiocytes, large mononuclear cells, and degenerating cells are sources of error.

CYTOLOGIC FEATURES

The cytologic features are similar to those of other epithelia. Cases of dysplasia, carcinoma in situ, and invasive carcinoma can be readily distinguished. The following is a brief description of the cytologic features of these lesions. Cells were obtained by decanting bile from the gallbladder immediately after cholecystectomy.

Dysplasia

Dysplastic cells desquamate in sheets, are less cohesive than normal epithelial cells, and exhibit some variation in size and shape. The nuclei are large, round, or ovoid, with well defined and uniformly stained nuclear membranes. The chromatin appears finely granular, and nucleoli are more conspicuous than in normal cells. As a consequence of an increase in nuclear volume, there is a moderate decrease in nuclear cytoplasmic ratio (figs. 125, 126). Goblet cells often show moderate nuclear atypia.

Carcinoma in situ

Cell aggregates tend to form sheets. Individual cells show great variation in size and shape and are less cohesive than in dysplasia. There is also considerable variation in size and shape of the nuclei. Their membranes are reinforced and do not stain uniformly. The chromatin becomes coarsely granular and irregularly distributed. The nucleoli are usually large, pleomorphic, multiple, and more prominent than in dysplasia. The nuclear volume is greatly increased, resulting in obvious loss of nuclear cytoplasmic ratio (fig. 127).

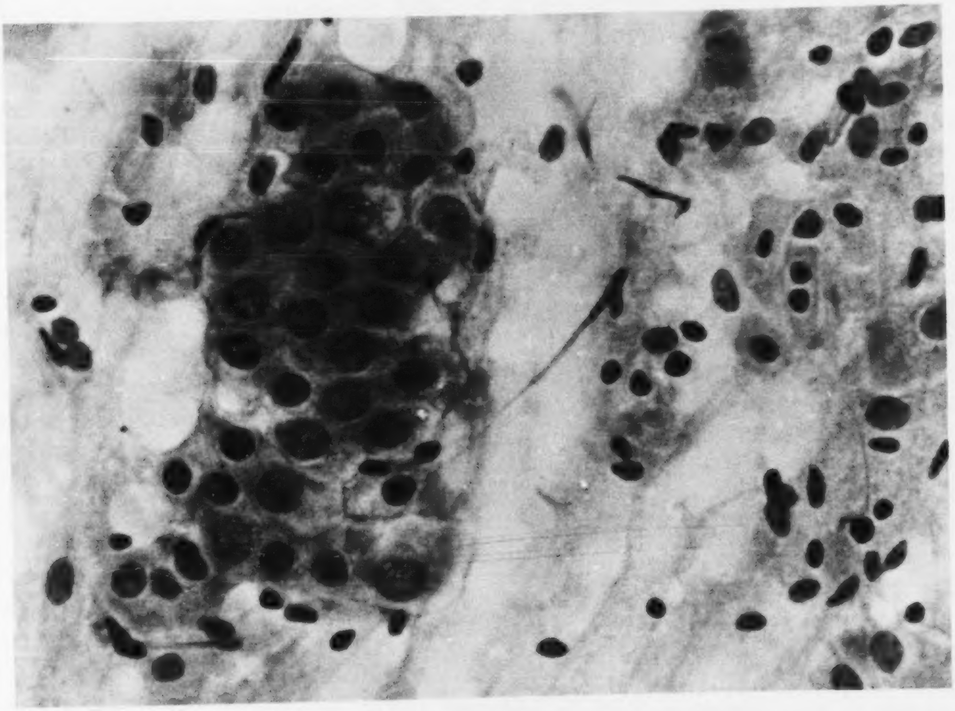

Figure 125
CYTOLOGY – SLIGHT DYSPLASIA
Sheet of dysplastic cells with some enlargement of nuclei and loss of normal nuclear-cytoplasmic ratio. The nuclei are round, have a finely granular chromatin and small nucleoli. X450.

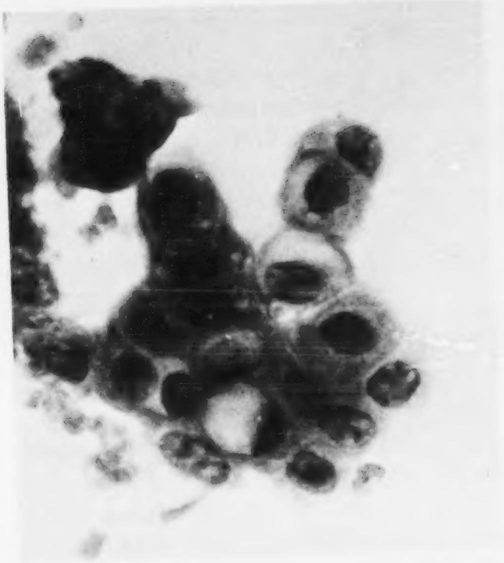

Figure 126
CYTOLOGY – MODERATE DYSPLASIA
Cluster of dysplastic epithelial cells. Goblet cells show moderate nuclear atypia. X500.

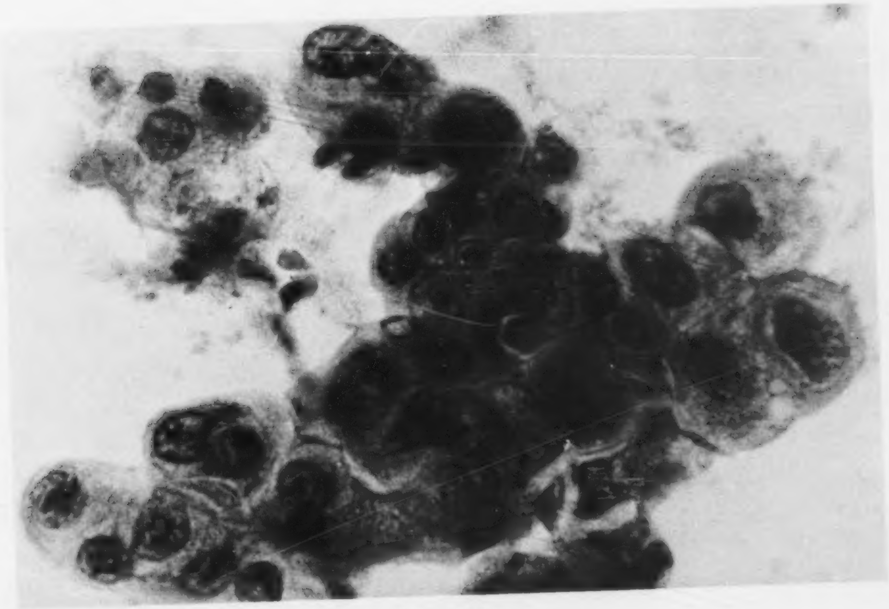

Figure 127
CYTOLOGY – CARCINOMA IN SITU
A sheet of neoplastic epithelial cells. Note great variation in size and shape of the cells. The chromatin is coarsely granular and unevenly distributed. Nucleoli are multiple, pleomorphic, and prominent. X500. (From Alonso-DeRuiz, P., Albores-Saavedra, J., Henson, D.E., and Monroy, M.N. Cytopathology of the precursor lesions of invasive carcinoma of the gallbladder. Acta Cytol. 26:144-152, 1982.)

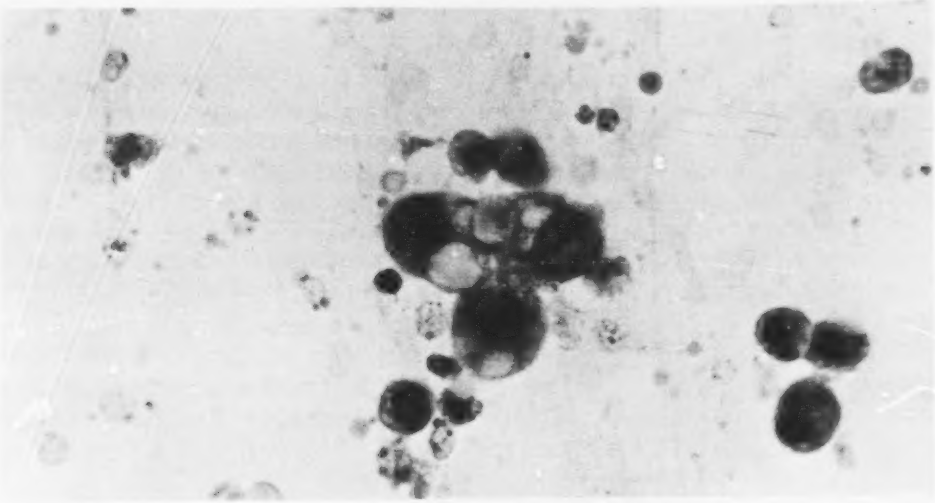

Figure 128

CYTOLOGY – WELL DIFFERENTIATED ADENOCARCINOMA

Small group of malignant epithelial cells with round nuclei, prominent nucleoli, and coalescent cytoplasmic mucin vacuoles. X400. (From Alonso-DeRuiz, P., Albores-Saavedra, J., Henson, D.E., and Monroy, M.N. Cytopathology of the precursor lesions of invasive carcinoma of the gallbladder. Acta Cytol. 26:144-152, 1982.)

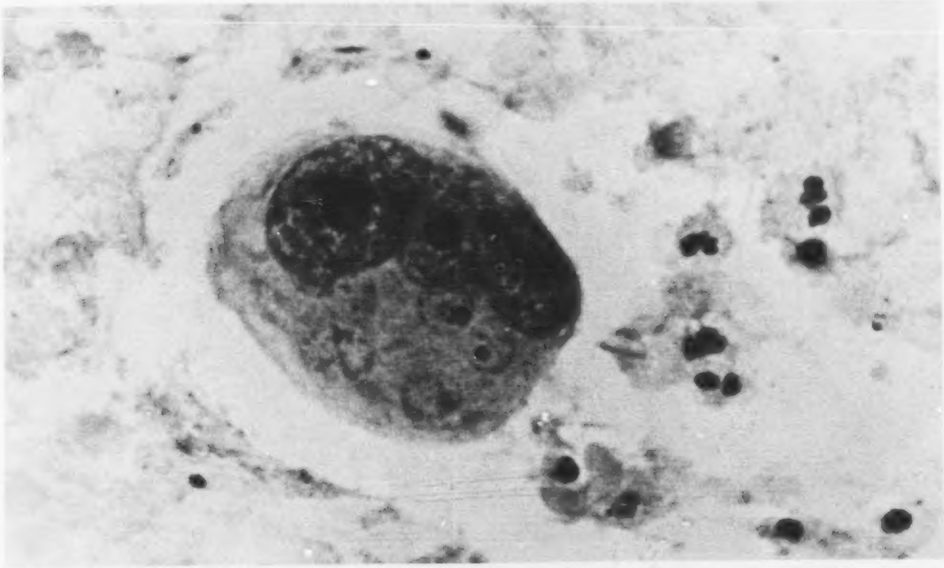

Figure 129

PLEOMORPHIC GIANT CELL ADENOCARCINOMA

A single Reed-Sternberg-like cell with several nuclei and macronucleoli is present. X500. (From Alonso-DeRuiz, P., Albores-Saavedra, J., Henson, D.E., and Monroy, M.N. Cytopathology of the precursor lesions of invasive carcinoma of the gallbladder. Acta Cytol. 26:144-152, 1982.)

Invasive Carcinoma

A tumor diathesis usually occurs in cases of invasive adenocarcinoma. Malignant cells desquamate either singly or in small clusters. Their cytologic features vary according to the type of tumor. Well differentiated adenocarcinomas show cells with round or ovoid nuclei and prominent nucleoli. These nuclei are vesicular or hyperchromatic. The cytoplasm is usually vacuolated (fig. 128). A papillary arrangement of neoplastic cells is highly suggestive of papillary carcinoma. In giant cell carcinoma, cellular pleomorphism is more pronounced than in other types. Giant neoplastic cells with one or several bizarre nuclei and prominent macronucleoli are seen (fig. 129). The cytologic characteristics of oat cell carcinomas are similar to those of the lung. The cells are small, but larger than lymphocytes. Often, their nuclei are large and hyperchromatic, or vesicular with fine chromatin granules and one or two small nucleoli. The cytoplasm may not be seen or may appear as a small perinuclear rim.

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TUMOR-LIKE LESIONS

There are a number of tumor-like lesions that occur in the gallbladder and extrahepatic bile ducts. Some of these lesions are inflammatory in nature and may be mistaken for neoplasms because of their gross features or appearance on cholecystograms. Others, such as adenomyomatous hyperplasia, may be confused with cancer histologically. With some exceptions, these lesions are asymptomatic and usually discovered in specimens removed for cholecystitis. Some are important because they may be precursors of cancer.

CHANGES IN CHOLECYSTITIS

The epithelial changes in chronic cholecystitis are not constant, but vary greatly in structure, severity, and topographic distribution. Moreover, their incidence is often a reflection of sampling, the number of sections examined, and the technic of study. We believe that pathologists should become familiar with these changes, otherwise an inexperienced observer may confuse them with carcinoma. It has been suggested that some of these lesions, especially intestinal metaplasia and squamous metaplasia, play an important role as precursors of carcinomas of the gallbladder (Laitio; Azadeh and Parai).

Epithelial Changes

Accelerated cell proliferation in the human gallbladder mucosa in cholelithiasis has been shown by autoradiography (Putz and Willems). Tritiated thymidine is incorporated into the epithelium of lithiferous gallbladders 23 times greater than normal. From a morphologic point of view, however, the most constant epithelial abnormality in cholecystitis is an increase in the number of mucin-producing cells (fig. 130).

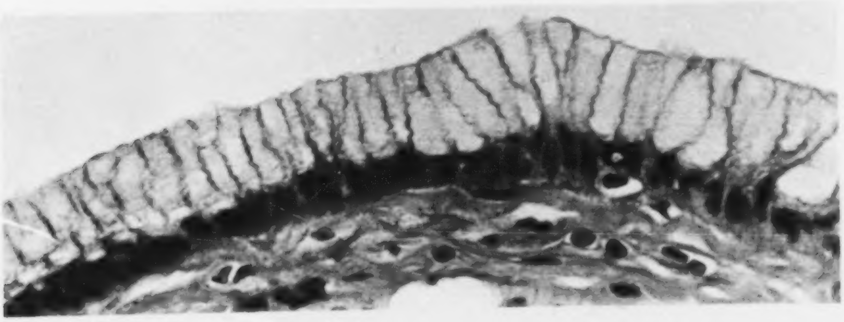

Figure 130
EPITHELIAL CHANGE IN CHOLECYSTITIS
The normal gallbladder epithelium has been replaced by mucin-producing cells. This is the most common epithelial change seen in chronic cholecystitis. X400.

In other words, there is a tendency for the epithelium to assume a greater secretory, rather than absorptive function (Fox; Hopwood et al.). Ulceration of the mucosa often occurs and is usually followed by epithelial regeneration. These regenerating cells can appear atypical, showing hyperchromatic nuclei, prominent nucleoli, basophilic cytoplasm, and even mitotic figures. These changes should not be mistaken for dysplasia or carcinoma in situ.

In addition, focal atrophic changes are often noted; the epithelium becomes cuboidal or flattened and loses microvilli. Other changes include pseudostratification and multilayering. Hyperplasia of the pencil-like cells can also occur in some cases (fig. 131). All these changes probably represent a reaction of the surface epithelium to injury (Fox).

Chronic cholecystitis, with or without ulceration, may be accompanied by proliferation of hypertrophic nerve bundles in the muscular and perimuscular connective tissue. Sometimes this change is so pronounced as to simulate a traumatic neuroma.

Rokitansky-Aschoff Sinuses

Rokitansky-Aschoff sinuses, or crypts, are epithelial invaginations that may penetrate the muscle layer and reach the perimuscular connective tissue (fig. 132). Occasionally visualized on cholecystograms, they are often seen in cases of chronic cholecystitis and less frequently in normal gallbladders. Their etiology and pathogenesis are still controversial (Elfving). Increased intraluminal pressure and a weak muscle

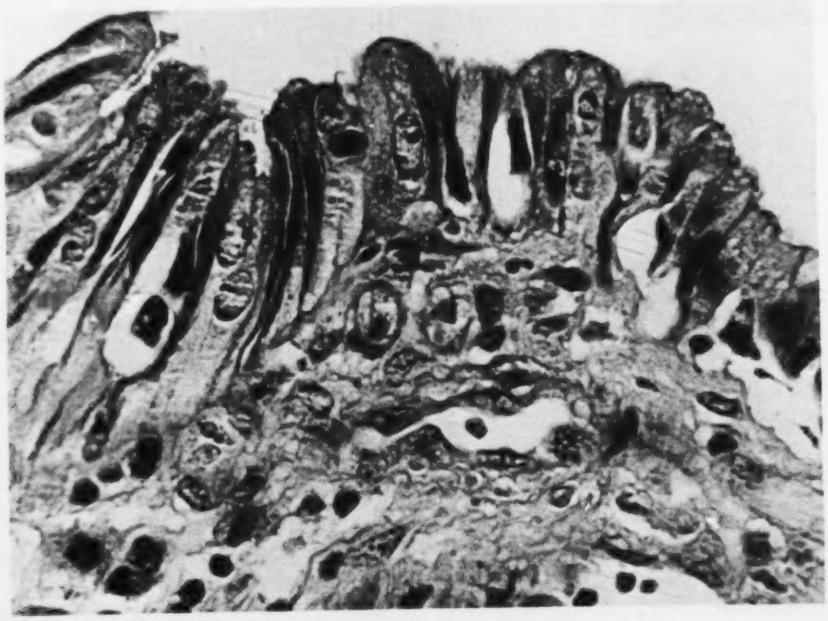

Figure 131
EPITHELIAL CHANGE IN CHOLECYSTITIS
An area showing an increased number of pencil-like cells. X460.

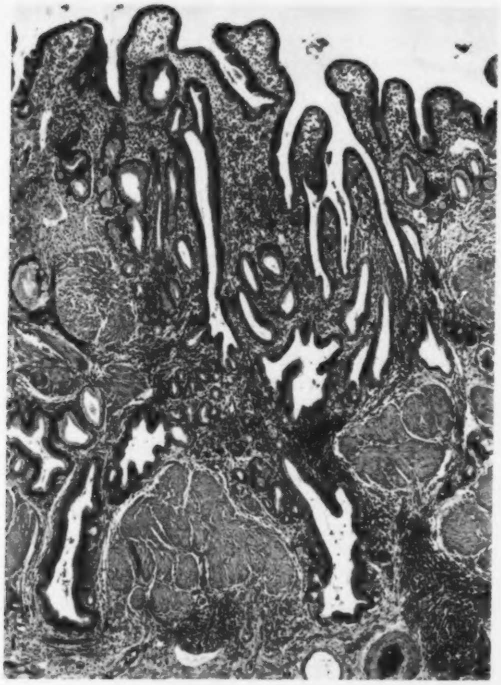

Figure 132
ROKITANSKY-ASCHOFF SINUS
The gallbladder mucosa has herniated through the muscle layer into the perimuscular connective tissue. The wall shows chronic inflammation. X35. (Fig. 5 from Fascicle 26, First Series.)

layer are thought to be important pathogenetic factors (Robertson and Ferguson).

Histologically, the sinuses are long and tortuous, tend to branch, and are lined by a single layer of columnar cells. It is unlikely they will ever be confused with a well differentiated adenocarcinoma. Occasionally, however, and especially in the neck of the gallbladder, the marked proliferation and branching of the epithelium may simulate glands and lead to an erroneous diagnosis of carcinoma (fig. 133). Important features in the differential diagnosis include the lack of nuclear pleomorphism and mitotic activity, lobular orientation, absence of invasion, and demonstration of a continuity between surface epithelium and crypts.

Inflammation and fibrosis of the gallbladder wall may obliterate segments of the sinuses, which become dilated or cystic because of retained secretions. Bile, cholesterol crystals, or even stones can also accumulate in the crypts.

Rokitanky-Aschoff sinuses are analogous to the diverticula that develop in other hollow viscera, such as in the colon or urinary bladder.

Intestinal Metaplasia

A high percentage of gallbladders excised for cholecystitis show focal areas of intestinal metaplasia (Laitio). When fully developed, this lesion consists of goblet cells, columnar cells with a brush border, Paneth cells, and endocrine cells (Jarvi and Lauren). The extent of metaplasia varies considerably, however, from only a few goblet cells to complete replacement of several mucosal folds by all four cell types. In some cases, only one or two cell types can be identified, especially in early lesions and when only hematoxylin and eosin stained sections are available (Laitio).

Metaplastic changes first appear at the tips of the mucosal folds, eventually progressing down the sides (fig. 134). Transitions from normal columnar cells to mature goblet cells and from columnar cells to cells with slender microvilli similar to those of the intestine were demonstrated by electron microscopy (Laitio and Nevalainen). We have also seen cells with both cytoplasmic mucin and Paneth granules. Glands lined by intestinal metaplastic epithelium may also be seen in the lamina propria.

Metaplastic epithelium contains several substances found in normal and abnormal

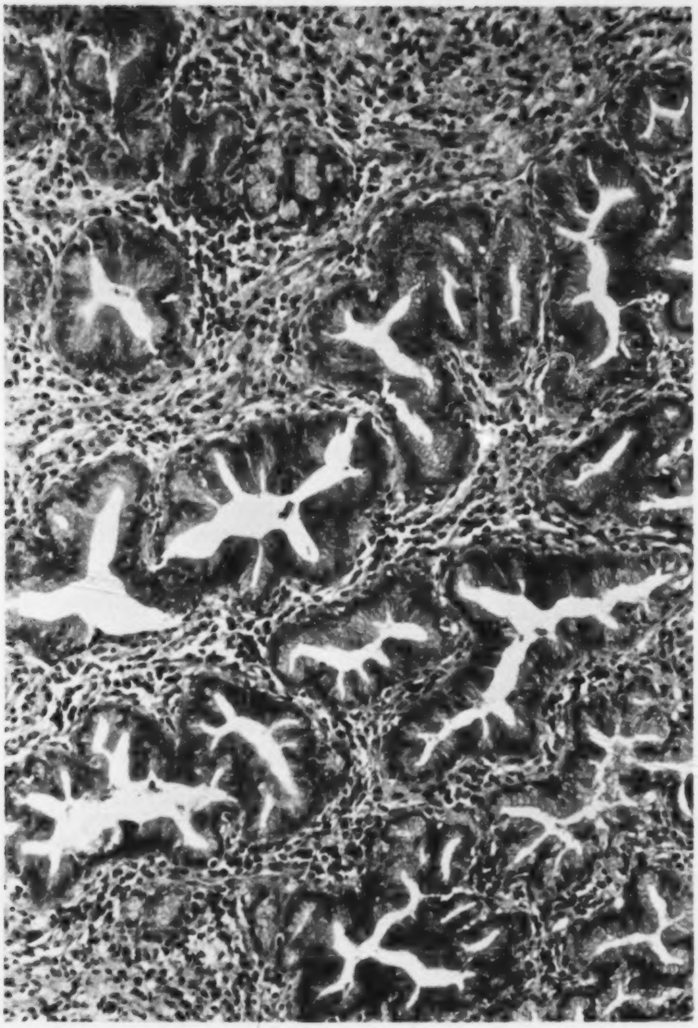

Figure 133
ROKITANSKY-ASCHOFF SINUS
Multiple epithelial invaginations have formed glandlike structures in the wall of the gallbladder. These areas should not be confused with a well differentiated adenocarcinoma. X150.

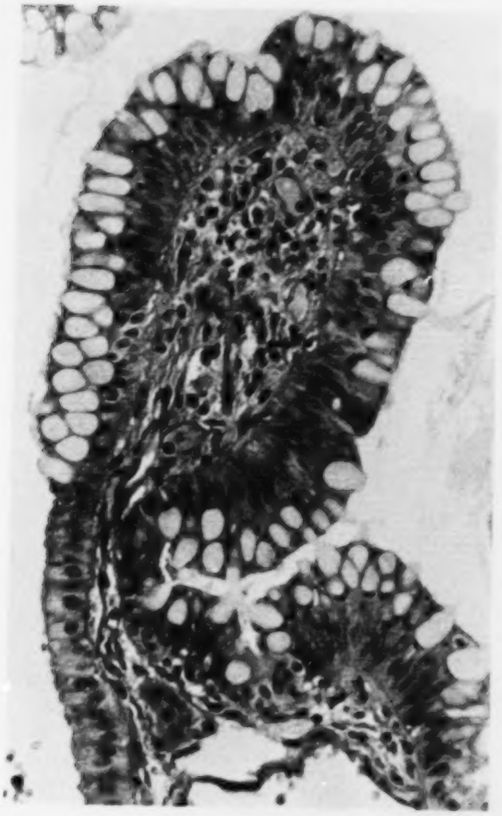

Figure 134
INTESTINAL METAPLASIA
The epithelium at the top and lateral sides of the mucosal fold has been replaced by mature goblet cells. Intestinal metaplasia first occurs at the top of the folds. X160.

intestinal epithelium. For example, metaplastic cells contain intestinal associated antigens (deBoer and Nairn; deBoer et al.), which also occur in the intestinal-type adenocarcinomas (Laitio and Hakkinen; deBoer et al.). They contain CEA (Albores-(Saavedra et al., 1983) and a neutral or acidic nonsulfated mucin (Laitio and Terho), which also occur in carcinomas of the gallbladder and intestine.

Several types of endocrine cells, including EC and ECl cells, have been described in metaplastic epithelium (Laitio and Nevalainen; Albores-Saavedra et al., in press). Intermixed with columnar and goblet cells, these endocrine cells rest on the basal lamina and are located near capillaries. They can be identified by the Fontana-Masson and Grimelius stains or by electron microscopy (figs. 135, 136). With immunohistochemical methods, we have found serotonin in the EC cells.

Intestinal metaplasia is frequently seen adjacent to intestinal-type adenocarcinomas. Although the significance of this proximity in the genesis of these tumors remains to be determined, it has been suggested that metaplastic epithelium is more susceptible to malignant transformation than normal mucosa (Laitio; Azadeh and Parai). We should point out, however, that intestinal metaplasia also occurs adjacent to other types of carcinomas. Until further evidence is available, it seems premature to conclude that intestinal metaplasia is a premalignant lesion.

We believe that intestinal metaplasia represents a response to injury and is analogous to the process of intestinalization that occurs in the stomach.

Squamous Metaplasia

Replacement of the surface columnar epithelium by squamous epithelium is an exceedingly rare lesion. We have seen four cases, all of which were associated with lithiasis. In one patient, the gallbladder showed only chronic inflammation. The other three patients had, in addition, a malignant tumor; two cases of squamous cell carcinoma, and one of malignant fibrous histiocytoma. Histologically, the squamous epithelium appeared to be mature, with a normal granular and keratin

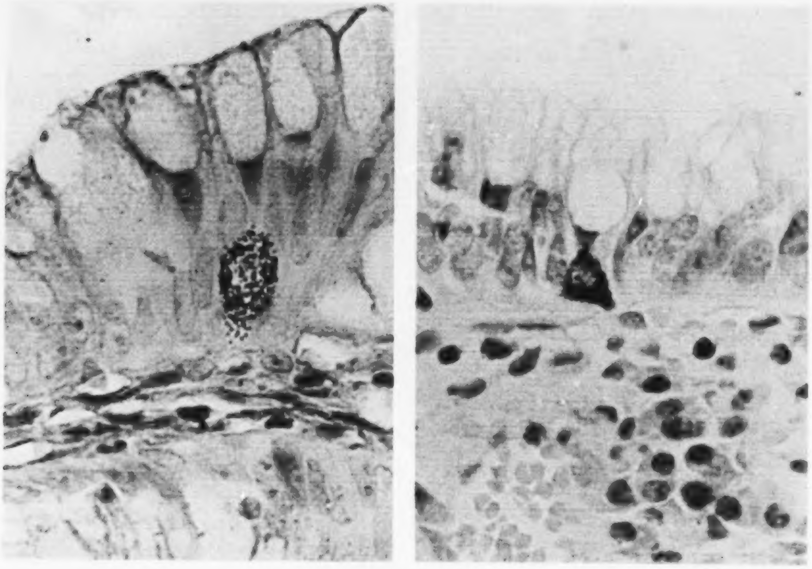

Figure 135
INTESTINAL METAPLASIA
Endocrine cells in areas of intestinal metaplasia. Argyrophil granules are seen in the cytoplasm of a cell located above the basement membrane (left). Grimelius stain. X680. On the right, argentaffin cytoplasmic granules are seen in a cell in a similar location. Fontana-Masson stain. X680.

layer (fig. 137). Focal progression to dysplasia and carcinoma in situ was observed in the two cases associated with the squamous cell carcinoma (fig. 138). All gallbladders showing squamous metaplasia should be carefully studied for incipient carcinoma.

Hyperplasia of Antral-Type Glands

It has been estimated that 10 to 50 percent of gallbladders with chronic inflammation exhibit hyperplasia of antral-type glands which may be found in the neck, lateral walls, or fundus (fig. 139; Laitio). The initial changes consist of branching of a crypt close to the base. Secondary budding occurs, forming more glands which may be arranged as poorly defined lobules or grow in a rather diffuse manner.

These glands are usually confined to the lamina propria, but occasionally may extend through the muscle layer to the serosa. They are lined by columnar cells with basal nuclei and a vacuolated cytoplasm which contains a nonsulfated acid mucin. In some cases, endocrine and Paneth cells are also found between these mucin-containing cells. Some of the endocrine cells are argentaffin, while others are arygrophil.

These antral-type glands which result from metaplasia are morphologically and histochemically distinct from the glands that normally occur in the neck. Hyperplasia of antral-type glands may coexist with fully developed intestinal metaplasia or with carcinoma.

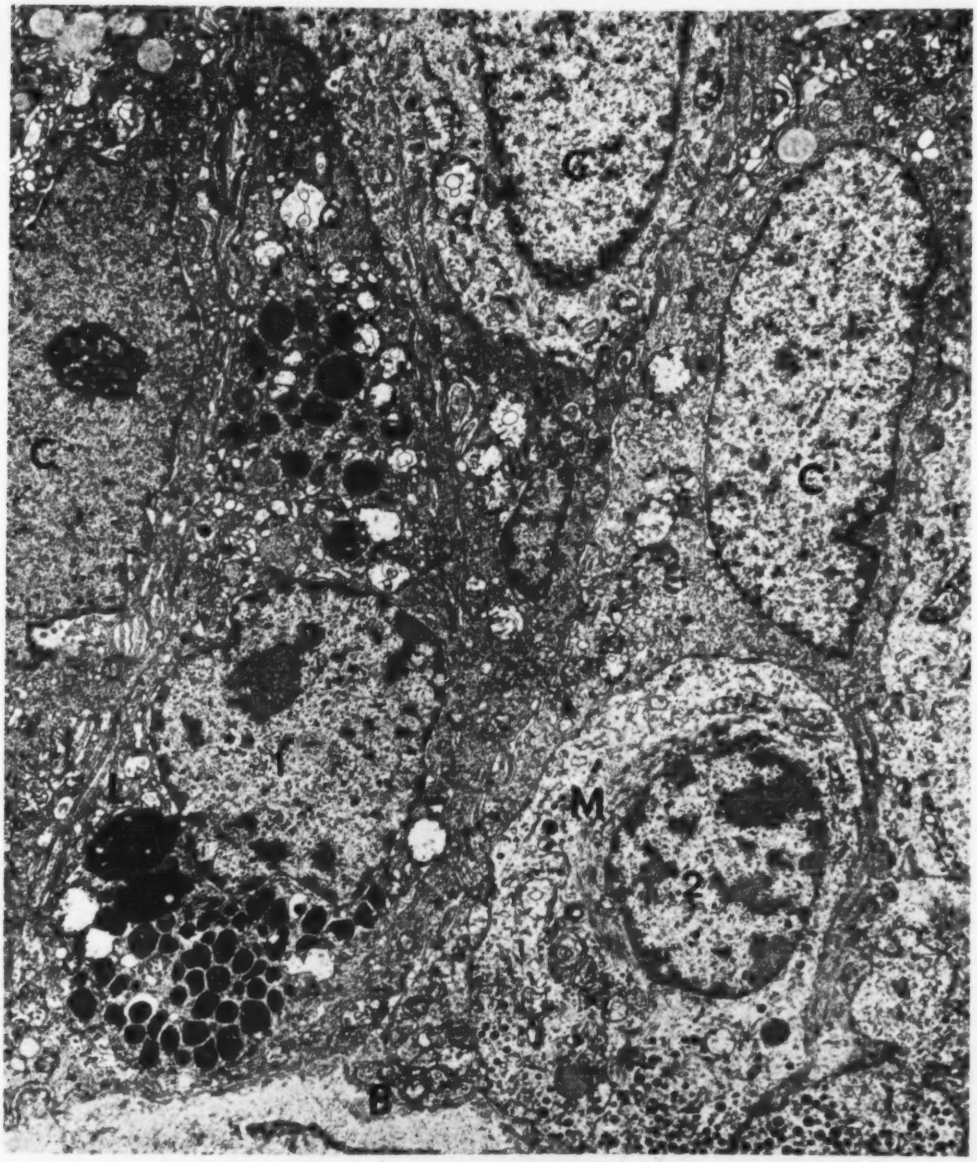

Figure 136
ULTRASTRUCTURE OF ENDOCRINE CELLS

Metaplastic gallbladder epithelial cells showing two types (types 1 and 2) of enterochromaffin cells. Both cells rest on the basal lamina (B). The secretory granules in the cell type 1 (EC) are large and slightly irregular in outline, whereas the secretory granules in the cell type 2 (ECl) are small and perfectly round. There are bundles of microfilaments (M) around the nucleus in the cell type 2 and large lysosomal dense bodies (L) in the cell type 1. Both enterochromaffin cells are closely associated with the columnar epithelial cells (C) of the gallbladder mucosa. X7000. (Courtesy of Dr. M. Laitio and Dr. T. Nevalainen, Finland.)

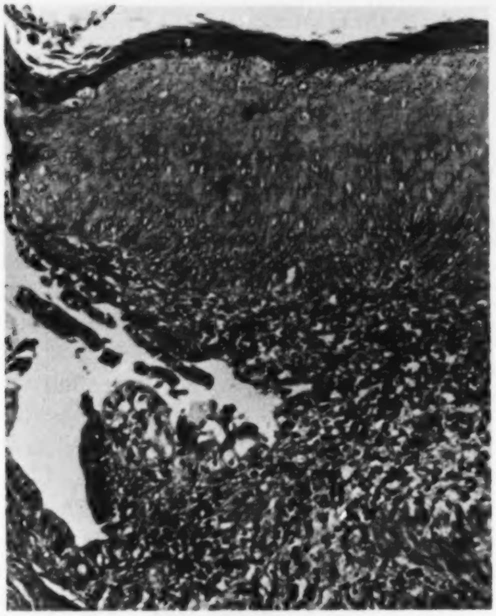

Figure 137
SQUAMOUS METAPLASIA
The gallbladder epithelium has been partially replaced by keratinized stratified squamous epithelium. Normal epithelium is seen on the left. Squamous metaplasia can involve large areas of the mucosa. X150. (Courtesy of Dr. J. Aguirre, Mexico City, Mexico.)

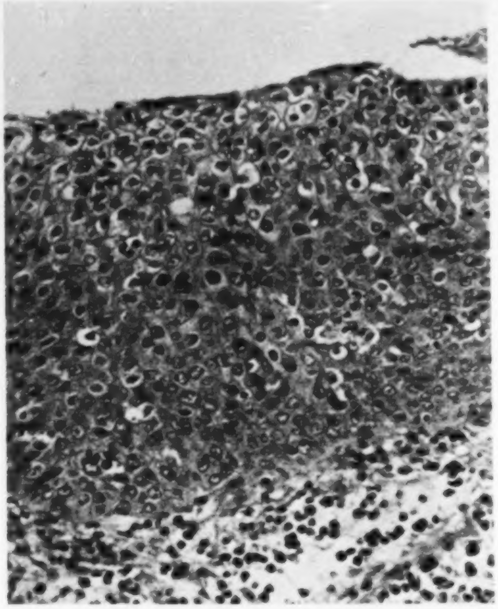

Figure 138
SEVERE SQUAMOUS DYSPLASIA
The metaplastic squamous epithelium shows atypical changes at all levels. Several mitotic figures are seen. X160.

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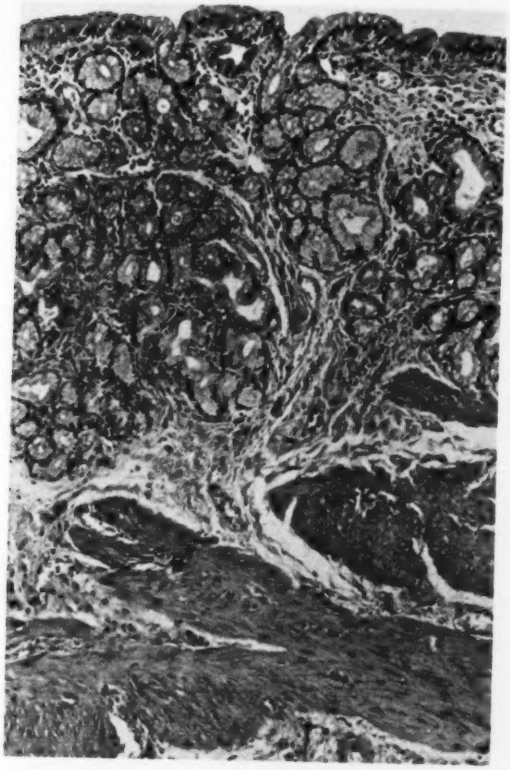

Figure 139
HYPERPLASIA OF ANTRAL TYPE GLANDS
Hyperplastic antral-type glands are arranged in lobules located in the lamina propria. This lobular pattern is common. X125.

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ADENOMYOMATOUS HYPERPLASIA

SYNONYMS AND RELATED TERMS: Adenomyoma; adenomyomatosis; cholecystitis cystica; cholecystitis glandularis proliferans; diverticulosis; Luschka's sinuses.

This type of hyperplasia, which is the most common, constituting more than 40 percent of all benign tumors and tumor-like lesions in the gallbladder (Christensen and Ishak), has no malignant potential (Fotopoulos and Crampton). According to the extent of involvement, it can be divided into three forms: localized, segmental, or diffuse. The diffuse type is often referred to as cholecystitis glandularis proliferans. Clinically, adenomyomatous hyperplasia may either be asymptomatic or produce symptoms indistinguishable from those of chronic cholecystitis. The disease is more common in adult women and can be visualized by cholecystography (Jutras and Levesque; Fotopoulos and Crampton).

The localized form, also known as adenomyoma, is the most common and is nearly always found at the tip of the fundus. Grossly, it appears as a well circumscribed, umbilicated nodule bulging into the lumen or projecting toward the serosal surface (fig. 140). The cut surface is composed of gray or yellow white rubbery tissue, with numerous small cystic spaces causing a honeycomb appearance. In the segmental and diffuse forms, there is a thickening of part of or the entire gallbladder wall and small cystic spaces (fig. 141).

The basic histologic changes consist of branching duct or glandlike structures in the wall of the gallbladder and hyperplasia of smooth muscle cells (fig. 142). The epithelial structures, which may contain

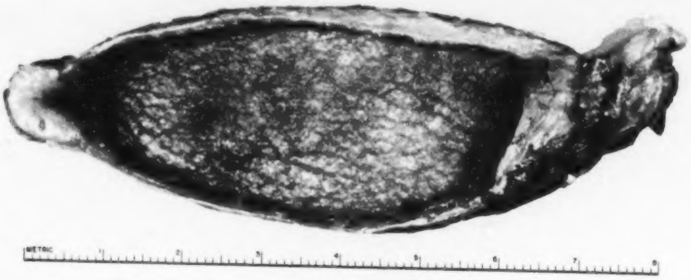

Figure 140
LOCALIZED ADENOMYOMATOUS HYPERPLASIA
The fundus of the gallbladder contains a gray white lesion with a central dimple and many small cysts. The remainder of the gallbladder appears normal. (Fig. 6 from Fascicle 26, First Series.)

inspissated bile, mucus, or stones, represent mucosal invaginations or outpouchings. Therefore, they are lined by a single layer of tall columnar cells similar to those on the surface epithelium (fig. 143). On occasion, subserial sections are needed to demonstrate continuity between the glandlike structures and the surface epithelium. Moreover, inflammation and fibrosis, which often accompany this lesion, can obstruct and even obliterate the epithelial lined spaces, making it difficult or impossible to demonstrate such a connection. Obstruction enhances dilatation of the distal portion of the glandlike structures, which may then become cystic (fig. 144). Secondary gland formation sometimes occurs in the form of small mucous glands. When these glands proliferate, they tend to form poorly defined lobules. The hyperplastic muscle bundles usually surround the glandlike structures, a feature which allows separation from Rokitansky-Aschoff sinuses. It is now accepted that asymptomatic patients do not require surgical treatment.

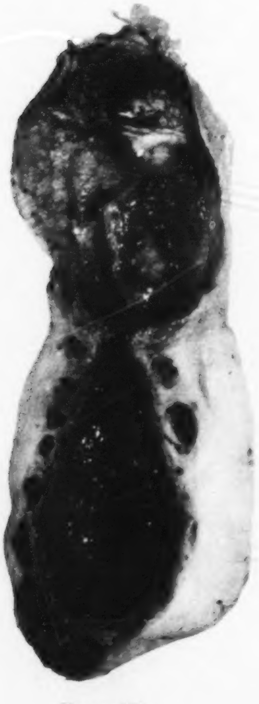

Figure 141
SEGMENTAL ADENOMYOMATOUS HYPERPLASIA
A sharply circumscribed adenomyomatous hyperplasia is separated from the normal part of the gallbladder by a stricture. The thick wall of the distal loculus contains cystic spaces in which there are many pigmented calculi. (Fig. 7 from Fascicle 26, First Series.)

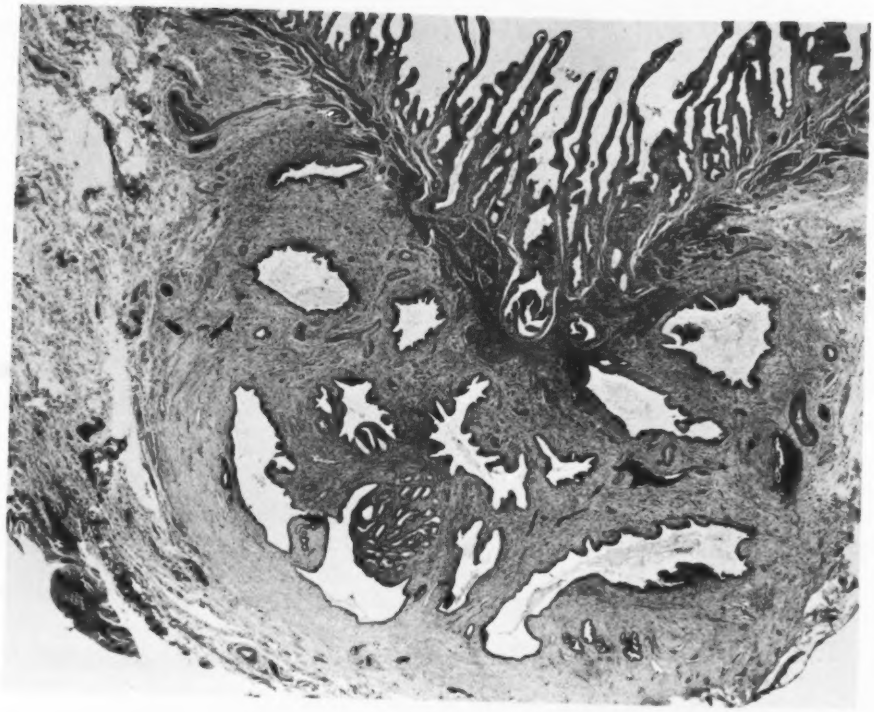

Figure 142
ADENOMYOMATOUS HYPERPLASIA
The characteristic architecture of adenomyomatous hyperplasia of the fundus is shown. Around the entrance of the ducts into the lumen of the gallbladder, there are many long folds of mucosa. Multiple cystic ducts, some with secondary centers of hyperplasia, lead from the central focus, through the wall of the gallbladder, into the subserosa. X6. (Fig. 8 from Fascicle 26, First Series.)

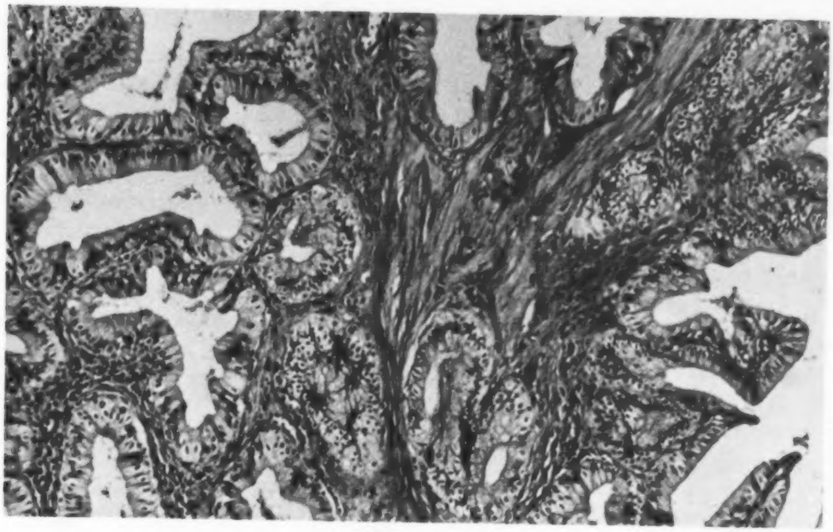

Figure 143
ADENOMYOMATOUS HYPERPLASIA
Closely packed glandlike spaces lined with columnar epithelium and surrounded by bundles of smooth muscle are seen in this localized type of adenomyomatous hyperplasia. The epithelial cells have a clear cytoplasm and basal nuclei. Lesion was present in the fundus of the gallbladder. X100.

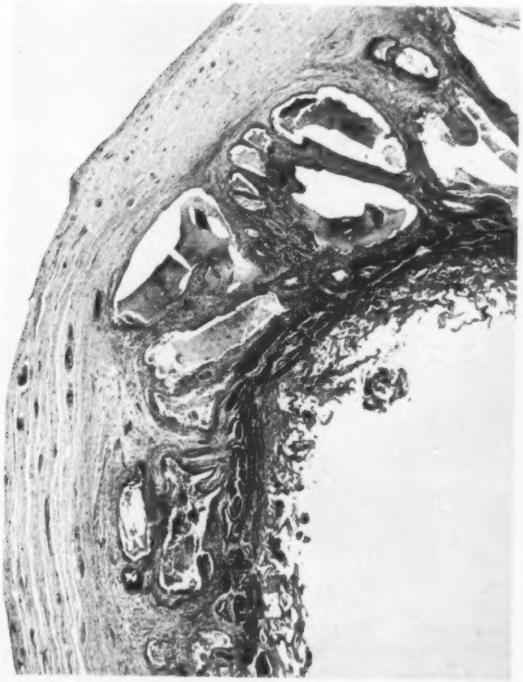

Figure 144
DIFFUSE ADENOMYOMATOUS HYPERPLASIA
In this diffuse type of hyperplasia, the cystic glands arise from the mucosa, but are most prominent in the subserosa. Some of the glands contain small calculi. X6. (Fig. 10 from Fascicle 26, First Series.)

LUSCHKA'S DUCTS

Luschka's ducts represent a common developmental anomaly found in gallbladders with or without inflammation and lithiasis. They are located primarily in the perimuscular connective tissue adjacent to the liver or, less frequently, on the serosal surface. They are usually multiple and communicate with the intrahepatic bile ducts or with the abdominal cavity when located on the serosal surface. It has been claimed that these ducts also communicate with the gallbladder lumen, particularly in the region of the neck (Beilby). Histologically, Luschka's ducts are lined by either a cuboidal or columnar biliary-type epithelium and surrounded by concentric rings of connective tissue, which differentiates them from deep Rokitansky-Aschoff sinuses (fig. 145). Luschka's ducts are small ectopic bile ducts that are laid down during embryologic development (Elfving).

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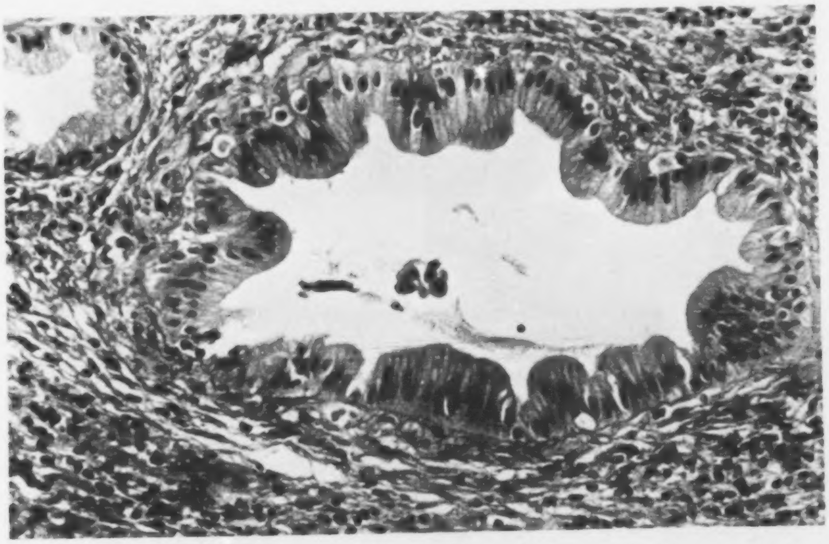

Figure 145
LUSCHKA'S DUCT

A Luschka's duct is lined by columnar biliary type epithelium and surrounded by concentric rings of collagen fibers. Some chronic inflammatory cells are also present in the surrounding fibrous tissue. Luschka's ducts are most common in the perimuscular connective tissue adjacent to the liver. X160.

PRIMARY PAPILLARY HYPERPLASIA

SYNONYMS AND RELATED TERMS: Adenomatous hyperplasia; primary hyperplasia.

This lesion, which involves only the mucosa, has no relationship to adenomyomatous hyperplasia. Grossly, there is focal or diffuse thickening of the mucosa, which appears granular. Histologically, primary papillary hyperplasia has a villous pattern and is characterized by an increased number of mucosal folds that are much longer than normal, irregular, and frequently branch (fig. 146). They are lined by tall, uniform columnar cells with little or no mucin (fig. 147). Occasionally, the folds seem to coalesce, producing a reticulated spongy pattern (fig. 148). Primary papillary hyperplasia is seen in gallbladders with or without stones and may cause symptoms. It occurs in both children and adults and probably is a true mucosal hyperplasia (Elfving et al.). We have seen a case associated with carcinoma of the colon.

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HETEROTOPIA

SYNONYMS AND RELATED TERMS: Ectopia; aberrant tissue.

Ectopic tissue is occasionally found in the gallbladder or bile ducts. Except for an occasional case of gastric or pancreatic heterotopia, it is usually not associated with clinical symptoms.

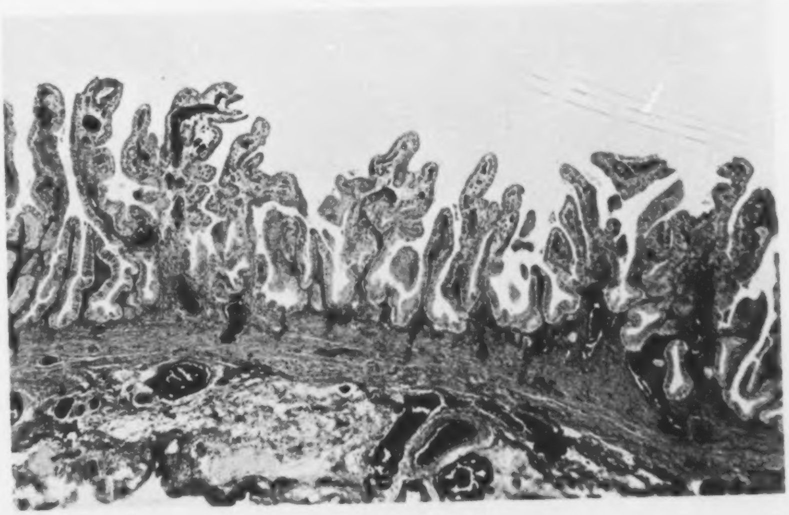

Figure 146
(Figures 146 and 147 from same patient)
PRIMARY PAPILLARY HYPERPLASIA
Low power view showing an increase in the number of mucosal folds, which have become taller and closer together. These changes may be focal or diffuse, covering large areas of the mucosal surface. X25.

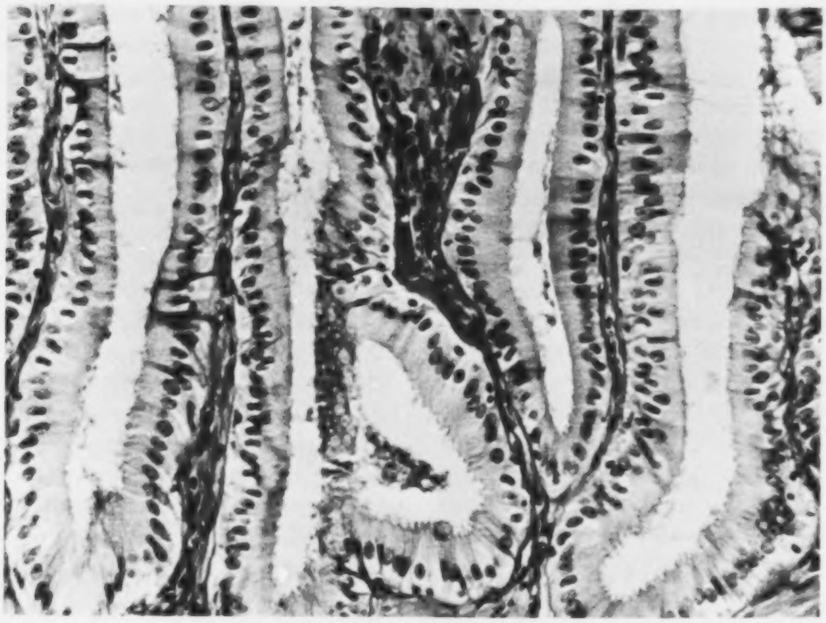

Figure 147
PRIMARY PAPILLARY HYPERPLASIA
Higher magnification of the mucosal folds, which are lined by tall columnar epithelium with basal nuclei. X250.

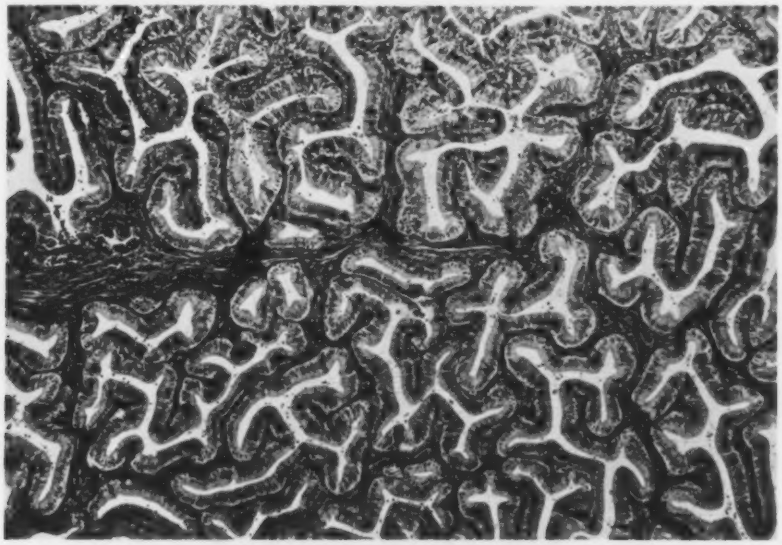

Figure 148
PRIMARY PAPILLARY HYPERPLASIA
In some cases, the folds are greatly increased, causing a spongy pattern. X160.

Gastric

Until 1979, 25 examples of ectopic gastric mucosa had been described in the biliary tree, the majority within the gallbladder. In most cases, the ectopic mucosa was located in the neck, although all parts of the gallbladder have been involved (Christensen and Ishak).

According to clinical and pathologic features, patients can be separated into two groups. One group, having no history of chronic cholecystitis and/or cholelithiasis, is composed of young adults and adolescents complaining of epigastric distress, right upper quadrant pain, nausea, and vomiting. These symptoms may be related to the number of acid secreting parietal cells (Runge et al.). In the other patient group, which is older, heterotopic gastric mucosa is usually an incidental finding in gallbladders excised for cholecystitis. Although ectopic gastric mucosa is considered to be a congenital anomaly, children are rarely affected.

Grossly, ectopic gastric tissue appears as an intramural gray white nodule, usually no greater than 2 cm in diameter and covered by an intact, often rugated mucosa. A well established peptic ulcer was recorded in the ectopic mucosa in two young patients (Gitlitz; Mooney et al.). Histologically, there may be pyloric, antral, or fundic type epithelium (figs. 149, 150). A transverse and circular smooth muscle layer under the gastric epithelium has been described in some reports (Williams and Humm; Mooney et al.). In patients in whom gastric glands and muscle are present, the normal gallbladder wall appears partially replaced by stomach. A unique case of dual heterotopia in which gastric mucosa and thyroid tissue coexisted in the wall of the gallbladder has also been documented (Curtis and Sheahan).

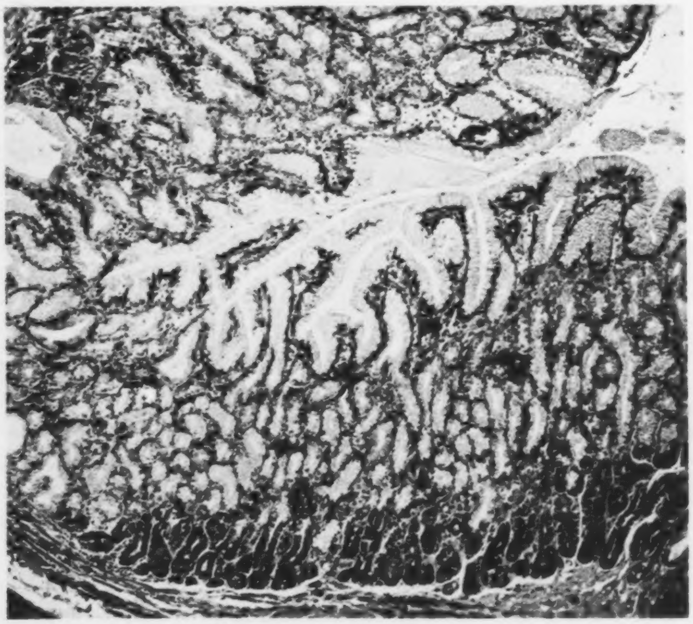

Figure 149
GASTRIC HETEROTOPIA
Fundic type gastric mucosa in the wall of the gallbladder. X60.

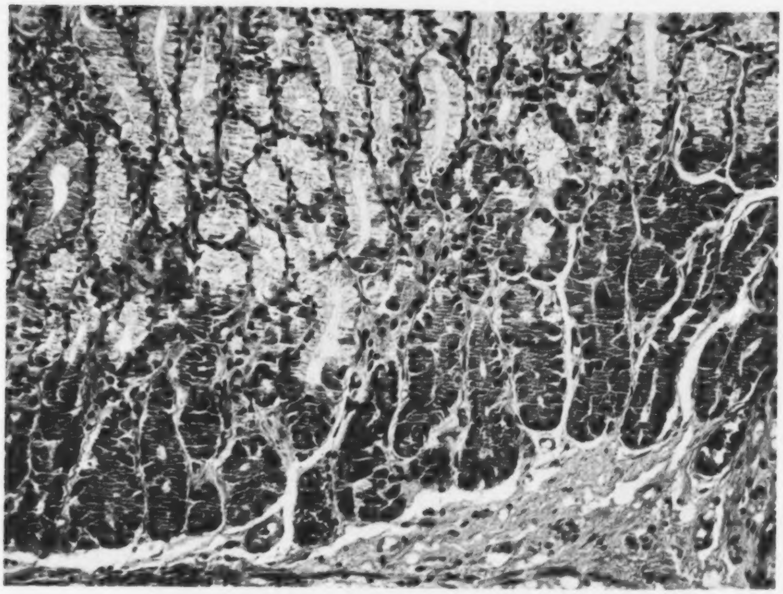

Figure 150
GASTRIC HETEROTOPIA
Detail showing parietal and chief cells lining gastric-type glands. X160.

Pancreatic

Pancreatic heterotopia, which occurs more often in the stomach, duodenum, or jejunum, is usually an incidental finding in the gallbladder (Elfving). Most patients are females, and only a few have symptoms. Gallstones are present in about one-third of patients. Grossly, the wall of the gallbladder may show only a focal thickening or contain a small yellow white nodule. Histologically, all the normal pancreatic structures are present – acini, small ducts, and islets of Langerhans (fig. 151). The small excretory ducts usually open into the lumen of the gallbladder.

Two patients with a clinical picture of acute pancreatitis have been reported (Vidgoff and Lewis; Qizilbash). Histologically, there was acute inflammation in the ectopic pancreas and fat necrosis in the wall of the gallbladder.

Hepatic

Ectopic liver is occasionally found on the serosal surface of the gallbladder (Bassis and Izenstark; Thorsness). Often discovered at laparotomy, the hepatic tissue consists of small encapsulated nodules supported by a mesentery from the gallbladder. The small fragments of normal liver torn away from the gallbladder bed during cholecystectomy should not be mistaken for ectopic liver.

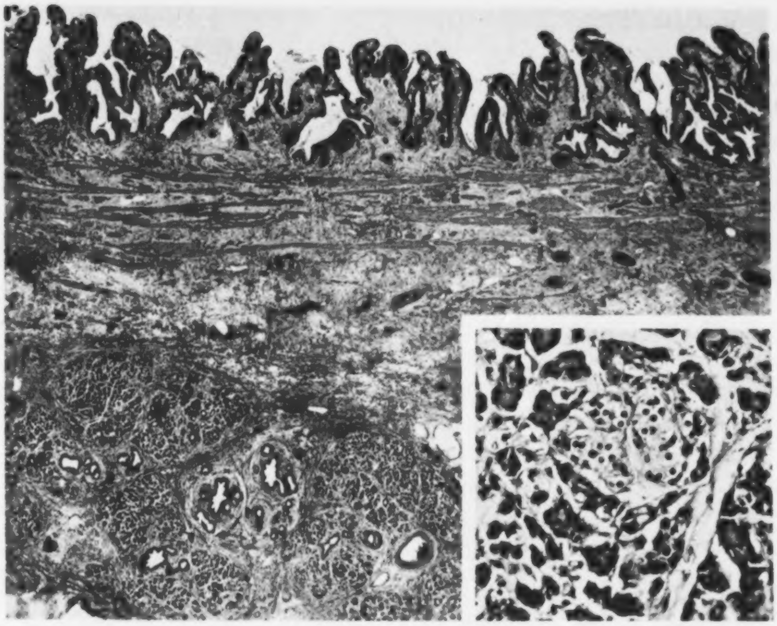

Figure 151
PANCREATIC HETEROTOPIA
A small focus of pancreatic tissue is present in the perimuscular connective tissue of the gallbladder. X15. Inset: An islet surrounded by pancreatic acini is seen. X160.

Adrenal Cortical

Nodular rests of ectopic adrenal cortex can occur in the subserosal fat of the gallbladder wall (Busuttil). Although accessory adrenal tissue is found in many sites, location in the gallbladder is unusual.

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POLYP

Polyps which can be mistaken for benign or malignant tumors on cholecystograms occur in the gallbladder. As with polyps elsewhere, they are classified according to their stromal elements. They have no malignant potential. Some pathologists may prefer to call these lesions pseudopolyps.

Cholesterol Polyp

Cholesterol polyps, which may be found in any area of the gallbladder, are small tumor-like projections attached to the mucosa by a pedicle. They are usually yellow, soft textured, multilobulated nodules that rarely exceed 1 cm in diameter. The larger ones are often seen on cholecystograms. These lesions can be associated with nonspecific symptoms, such as indigestion and right upper quadrant pain, but in only a small number of cases are they associated with lithiasis or cholesterolosis. Microscopically, they are composed of foamy histiocytes which are positive with oil red O and contain cholesterol. They are covered by a single layer of columnar cells similar to those lining adjacent mucosa (fig. 152). Most likely, these polyps are enlarged and distended villi which become pedunculated because of the accumulation of histiocytes.

Inflammatory Polyp

These are small polypoid lesions that can be single or multiple and are always associated with chronic cholecystitis. Because of their small size, 3 to 5 mm, and associated inflammatory changes, they are seldom visualized by cholecystography. The edematous connective tissue stroma contains inflammatory cells, small dilated blood vessels, and hyperplastic epithelial invaginations. These polyps appear to be the result of enlargement and fusion of villi due to chronic inflammation.

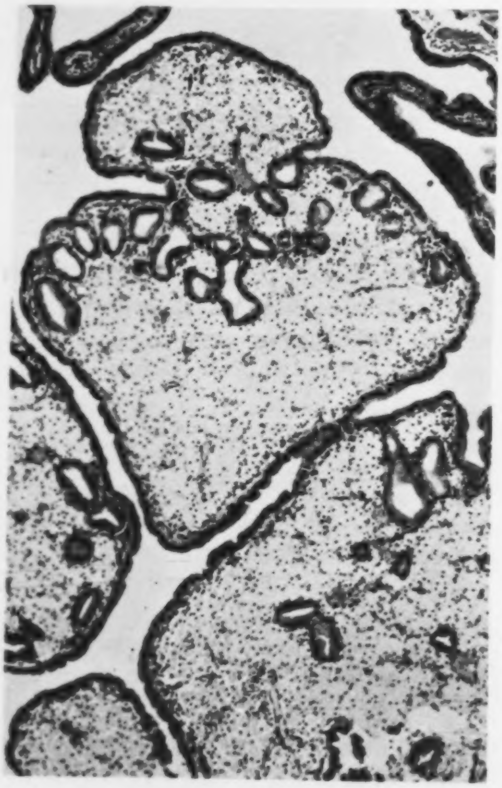

Figure 152
CHOLESTEROL POLYP
Several polypoid structures lined by normal gallbladder epithelium contain foam cells in the stroma. X60.

XANTHOGRANULOMATOUS CHOLECYSTITIS

SYNONYMS AND RELATED TERMS: Ceroid granuloma; fibroxanthogranuloma.

This type of inflammatory response may grossly simulate a malignant tumor, since it appears as a poorly defined, yellow, nodular mass which often extends through the wall of the gallbladder and may even protrude into the lumen. It is most commonly seen in adult women with gallstones.

Histologic sections show sheets of foamy histiocytes (which give a positive reaction to oil red O), lymphocytes, and plasma cells (fig. 153.). In addition, polymorphonuclear leukocytes, foreign body type giant cells, fibroblasts, and bands of collagen may also be present (fig. 154). The histiocytes may contain bile or ceroid pigment (Amazon and Rywlin). Occasionally they have a coarsely granular eosinophilic cytoplasm that is strongly PAS positive. Intracellular and extracellular iron pigment, presumably the result of old hemorrhage, can be demonstrated in many cases. Although this lesion can resemble malacoplakia, we were not able to demonstrate Michaelis-Gutmann bodies in any of our 37 cases. However, a

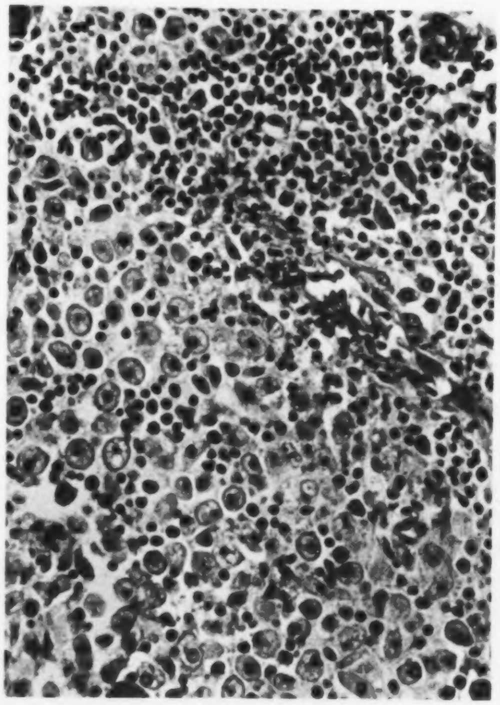

Figure 153
XANTHOGRANULOMATOUS CHOLECYSTITIS
Xanthogranulomatous cholecystitis showing foamy histiocytes mixed with lymphocytes, plasma cells, and foreign body giant cells. X200.

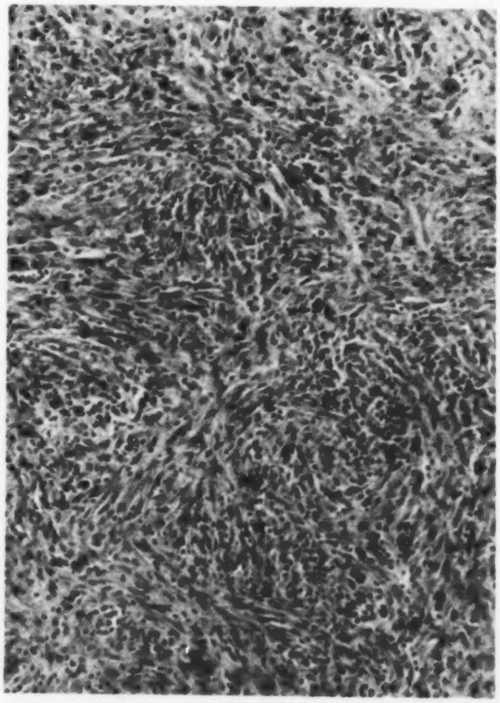

Figure 154
XANTHOGRANULOMATOUS CHOLECYSTITIS
Fibroblasts and histiocytes are arranged in bundles and, in some areas, they produce a storiform pattern. Chronic inflammatory cells, mainly lymphocytes and a multinucleated giant cell, are also present. This storiform pattern may lead to confusion with a fibrous histiocytoma. X140.

case of malacoplakia of the gallbladder has been reported (Charpentier et al.). Xanthogranulomatous cholecystitis can coexist with carcinoma.

The pathogenesis of this lesion is obscure, although it has been suggested that it results from ruptured Rokitansky-Aschoff sinuses (Goodman and Ishak). Histologically, it is similar to xanthogranulomatous pyelonephritis. Many cases are erroneously diagnosed as the ordinary type of chronic cholecystitis (Goodman and Ishak).

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PSEUDOLYMPHOMA

A small number of gallbladders with stones and chronic inflammation show hyperplasia of lymphoid tissue organized into follicles with germinal centers (cholecystitis follicularis). Rarely is the reactive lymphoid hyperplasia so prominent as to justify the designation of pseudolymphoma.

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HANDLING THE SURGICAL SPECIMEN
(Therapeutic Considerations)

In view of the fact that gallbladder carcinoma may not be evident grossly (Frank and Spjut), proper handling of routine cholecystectomy specimens is important in order to insure maximum treatment for patients found to have unsuspected carcinoma. This is especially true for older patients who are at greater risk and in areas where the incidence of gallbladder carcinoma is high. The following guidelines developed at the Mexico City General Hospital have proven useful to the pathologist and helpful to the surgeon in making therapeutic decisions:

1. The gallbladder should be opened immediately following cholecystectomy and the bile decanted into a beaker or centrifuge tube for cytology.

2. The specimen should then be inspected and frozen or paraffin sections prepared from any area suspicious of malignancy.

3. At least three sections, one from the fundus, one from the body, and one from the neck, should be submitted if no gross lesions are found.

4. The decanted bile should be studied for malignant cells (see p. 125). This procedure complements the information obtained from routine histologic sections.

In either frozen or permanent sections, it is important to determine the level of invasion and histologic type when carcinoma is present.

Carcinoma in situ (T_{is}) should be studied as in other organs, with multiple sections or sectioning the entire specimen by the "Swiss Roll Method" (Knudtson), in order to exclude invasive cancer. If none is found, no further treatment is recommended (Bivins et al.).

In cases of carcinoma extending only in the lamina propria (T1) and without lymph node metastasis, a simple cholecystectomy seems sufficient to cure the great majority of these patients (Nevin et al.). However, some consider simple cholecystectomy for Stage T_{is} and T1 cancers inadequate and recommend radical surgery for all lesions (Berdahl).

If invasive carcinoma extending to the perimuscular connective tissue or serosa (Stage T2) is seen in histologic sections, a wedge resection of the liver at the level of the gallbladder fossa with regional lymph node dissection should be advised (Weiskopf and Esselstyn). For carcinomas limited to the free surface of the gallbladder, a wedge resection may not be necessary (Adson).

In patients with gross tumor extension to the gallbladder fossa, microscopic confirmation by frozen section is necessary, especially if extensive resection including right hepatic lobectomy is planned (Pack et al.; Brasfield). However, the possibility of increasing survival in these patients is minimal (Piehler and Crichlow). The same is true for patients with neoplastic extension to the colon, duodenum, or stomach, in whom a partial resection of these organs can also be accomplished.

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BENIGN TUMORS OF THE EXTRAHEPATIC BILE DUCTS

Benign tumors and tumor-like lesions can develop in any segment of the extrahepatic bile ducts. They include: **adenomas,** which can be single or multiple, papillary, or tubular; **benign mesenchymal tumors; amputation neuromas,** and **heterotopias.** Multiple papillomas, or papillomatosis, is considered a precancerous lesion and is discussed separately.

Benign tumors can obstruct the extrahepatic ducts, requiring surgical intervention. Clinical differentiation from malignant tumors may be difficult, although diagnosis can often be suspected on the basis of cholangiography and selective angiography.

Adenomas are the most common tumor, while benign mesodermal tumors are extremely rare. Most of the benign tumors occur in the common duct or ampullary region (Chu; Barber et al.).

Clinically, the signs and symptoms tend to progress slowly, often over years. The most frequent finding is obstructive jaundice, occurring in more than 70 percent of patients. Usually the jaundice has an insidious onset and can be intermittent or persistent. Often there is pain and various gastrointestinal complaints. Because of obstruction, the liver may become enlarged and, provided the obstruction occurs below the cystic duct, the gallbladder may also become distended.

Most of the tumors are not large and can rarely be palpated. The largest recorded tumor, which weighed 750 grams, was found in the common duct of a four year old child (Leriche). Unless new lesions develop, the prognosis for a single benign tumor, especially located in the distal extrahepatic ducts, is excellent following surgery. Since these tumors may be multifocal, complete excision is the preferred treatment (Hulten et al.).

Incidence. Benign tumors of the extrahepatic bile ducts are uncommon (Chu). Most of our information is based on case reports. Many tumors are asymptomatic and discovered during surgery for other reasons or at the time of autopsy. In one study, asymptomatic polyps were found at the duodenal papilla in 4 of 100 consecutive autopsies (Baggenstoss).

ADENOMA

SYNONYMS AND RELATED TERMS: Adenofibroma; fibroadenoma; papilloma; polyp.

Since the extrahepatic bile ducts and gallbladder are composed of the same tissues, they produce similar tumors. Tubular, papillary, and mixed adenomas occur in the bile ducts as in the gallbladder. The incidence of each type is difficult to estimate, however, because many terms have been used to designate these tumors. As with adenomas in the gallbladder, bile duct adenomas can also show focal in situ malignant changes.

As expected, the histologic features of extrahepatic bile duct adenomas do not vary from those of gallbladder adenomas. Grossly, they are small, pedunculated or sessile pink white nodules. Microscopically, they contain either compact glands or papillary structures lined by columnar cells, or, rarely, both (figs. 155, 156).

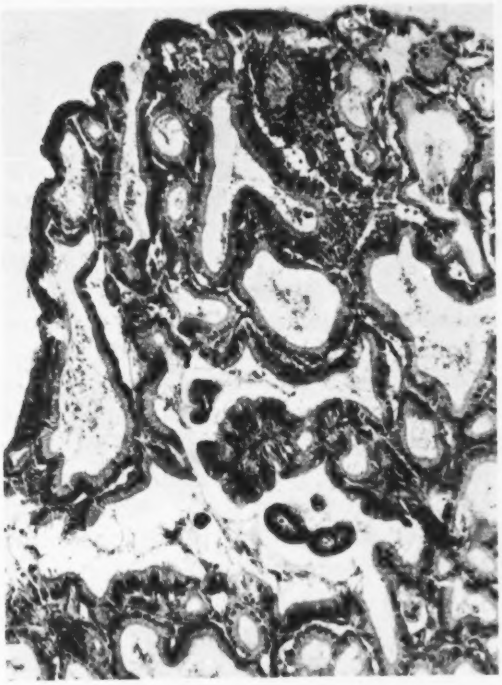

Figure 155
MIXED ADENOMA
Mixed adenoma of the common bile duct composed of mucus-secreting glands and small papillary structures, both of which are lined by columnar and cuboidal epithelium. The connective tissue stroma is minimal. X125. (Fig. 81 from Fascicle 26, First Series.)

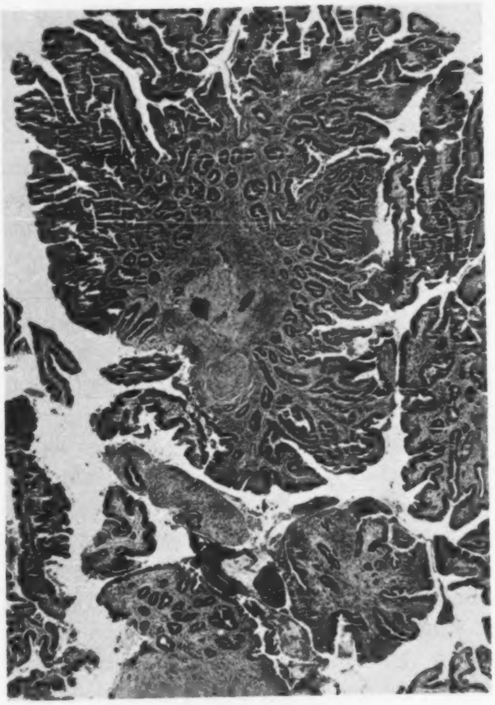

Figure 156
PAPILLARY ADENOMA
OF THE COMMON BILE DUCT
Multiple small papillary structures are oriented about a central fibrous stalk. X25.

From an analysis of 88 extrahepatic bile duct tumors, 65 percent were found in the common bile duct, 12 percent in the common hepatic duct, 7 percent in the cystic duct, 8 percent in the left hepatic duct, 1 percent in the right hepatic duct, 2 percent in multiple sites, and 5 percent were unspecified (Burhans and Myers).

Some clinicopathologic differences exist between adenomas of the extrahepatic bile ducts and those of the gallbladder. For example, these tumors are much less common in the extrahepatic ducts than in the gallbladder, although no reliable incidence figures are available. The fact that the mucosal surface of the gallbladder is 50-100 times greater than that of the extrahepatic bile ducts may account for this difference. Adenomas of the gallbladder are usually asymptomatic, whereas those occurring in the extrahepatic ducts often cause obstruction. Despite obstruction and bile stasis, the incidence of stones associated with bile duct adenomas is lower than that reported for benign tumors of the gallbladder. Finally, ulceration and massive hemorrhage from these bile duct tumors have been observed.

Although percutaneous transhepatic cholangiography, selective angiography, ultrasound examination, retrograde cholangiography, and computed axial tomography have increased the diagnostic accuracy of extrahepatic bile duct adenomas, the results of surgical treatment, on the other hand, have been somewhat disappointing. In some series, the incidence of local recurrence approaches 25 percent and the operative mortality 20 percent. Nearly one-fourth of these tumors are located in the proximal extrahepatic ducts, making their removal difficult and often impossible without a major hepatic resection. Many surgeons are reluctant to open and fully explore the bile ducts, a procedure necessary for complete excision. Finally, some of these tumors are multicentric.

Histologically, it is not possible to predict whether adenomas will recur or whether they are multicentric in origin.

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CYSTADENOMA

SYNONYMS AND RELATED TERMS: Hamartoma.

Cystadenoma of the extrahepatic bile ducts is a rare but distinctive neoplasm, similar to that occurring in the liver or pancreas. In fact, cystadenomas of the pancreas and bile ducts may coexist in the same patient (Keech). Most cystadenomas, however, are found only in the liver. Multiple intra- and extrahepatic cystadenomas have been reported (Ishak et al.). In the extrahepatic system, these tumors most often occur in the common duct, although we have seen a case in the gallbladder. They can cause bile duct obstruction and jaundice (Ansari et al.). Their size has varied from 1.5 to 6 cm. They are round or ovoid, with a smooth external surface. The lesion is usually a multiloculated thin walled cyst containing mucinous or serous fluid. In general, the walls of the individual locules measure 1 to 2 mm and their inner surfaces are smooth and glistening.

Microscopically, the locules are lined by a single layer of cuboidal or columnar cells that stain positive for mucin. The wall is composed of connective tissue that has a resemblance to ovarian stroma (fig. 157). In some areas, the connective tissue is loose and edematous, while in others it may be hyalinized. A variable number of macrophages laden with hemosiderin or lipofuscin are present in many cases. Smooth muscle cells are also observed in a few tumors. Small papillary folds lined by epithelium may project into the lumen of the cysts (fig. 158).

These benign tumors can recur following surgical removal because of incomplete excision or multicentric growth (Rogers; Barber et al.). Their malignant potential is,

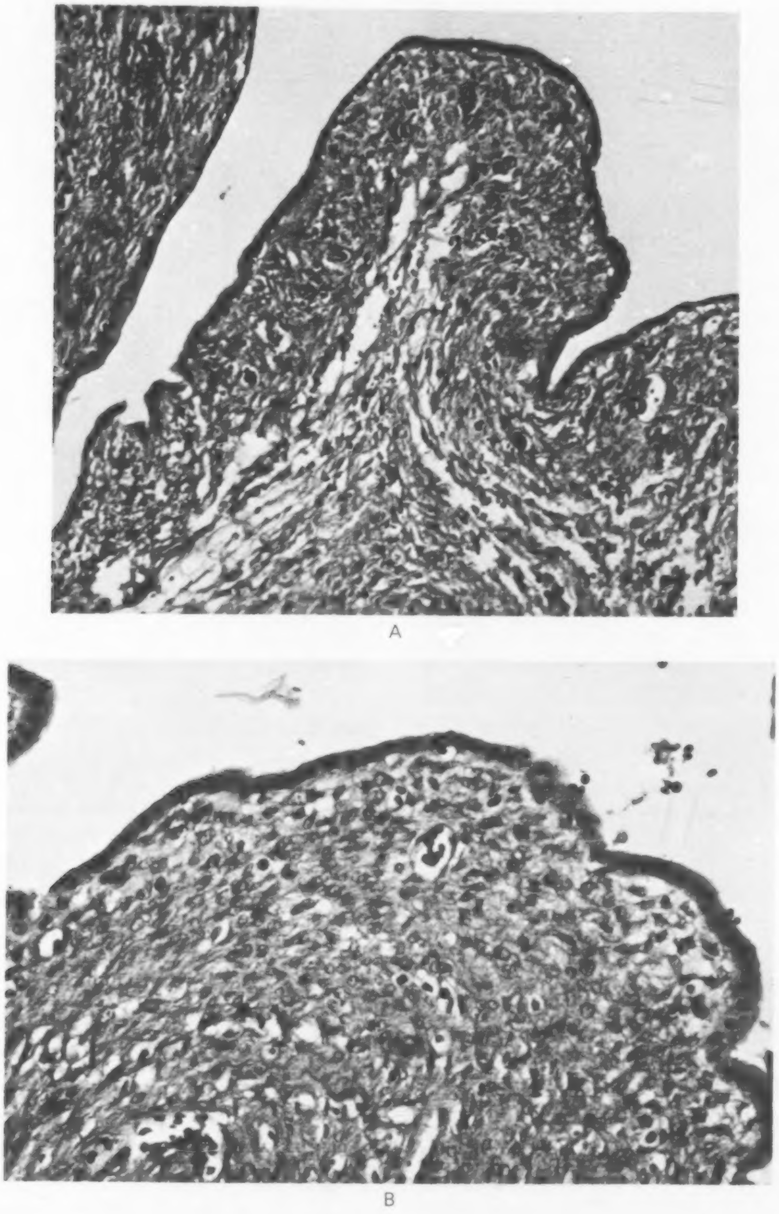

Figure 157
CYSTADENOMA OF THE COMMON BILE DUCT

(A) Low magnification of a papillary structure. The epithelial lining varies from low cuboidal to columnar. The stroma beneath the epithelium is cellular and resembles ovarian stroma. Deeper, the stroma is more fibrotic. X60. (B) The surface epithelium is cuboidal and the stroma is cellular and resembles ovarian stroma. X250.

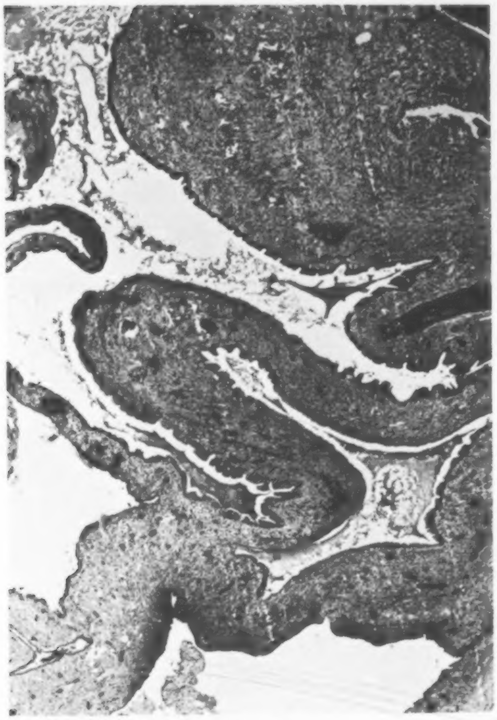

Figure 158
CYSTADENOMA OF THE GALLBLADDER
Low power photograph shows the wall of the cyst with complex folds. X38. (Courtesy of Dr. L. Rabin, Washington, DC.)

however, unknown. Malignant transformation of the epithelial lining does occur with intrahepatic cystadenomas (Marsh et al.; Ishak et al.; Woods).

Although the connective tissue in the wall resembles ovarian stroma, there are no reports of ectopic ovarian tissue occurring in the biliary tree.

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GRANULAR CELL TUMOR

SYNONYMS AND RELATED TERMS: Granular cell myoblastoma.

Granular cell tumors are almost limited to the cystic, hepatic, and common bile ducts. Rarely is the gallbladder the site of origin (Farris and Faust; Ishii et al.). Adult black females are most commonly affected. There is one report of a granular cell tumor occurring in the common duct in an 11 year old boy (Zvargulis et al.).

Signs and symptoms depend on the location of the tumor. In the extrahepatic or common bile ducts, it can cause obstructive jaundice, hepatomegaly, and right upper quadrant tenderness (Jain et al.; Whisnant et al.).; if situated in the gallbladder or cystic duct, right upper quadrant pain is the most common manifestation. Occasionally, a granular cell tumor of the biliary tree may coexist with one or more granular cell tumors in other sites, especially in the skin (Assor; Manstein et al.). Both single and multicentric granular cell tumors behave in a benign fashion.

Granular cell tumors are poorly circumscribed, firm, yellow tan in color, and usually no greater than 2 cm in diameter. They are composed of sheets or clusters of large ovoid or round cells separated by thin fibrous bands. The cells have a granular eosinophilic cytoplasm, which is PAS positive, and small uniform nuclei (fig. 159). These tumors usually compress the lumen of the bile duct as they infiltrate the wall (fig. 160). A granular cell tumor of the cystic duct can cause a mucocele in the gallbladder (Ruel et al.; Christensen and Ishak).

The preoperative diagnosis of this tumor is difficult. Most lesions are first discovered on frozen section. However, this diagnosis should be suspected when a patient with bile duct obstruction has a history of granular cell tumor, especially in the visceral organs. In our review, we found 29 patients with granular cell tumors in the biliary tract. In 15 of these patients, the tumor had occurred in the common duct. Multiple granular cell tumors have also been seen in the biliary tree (Aisner et al.).

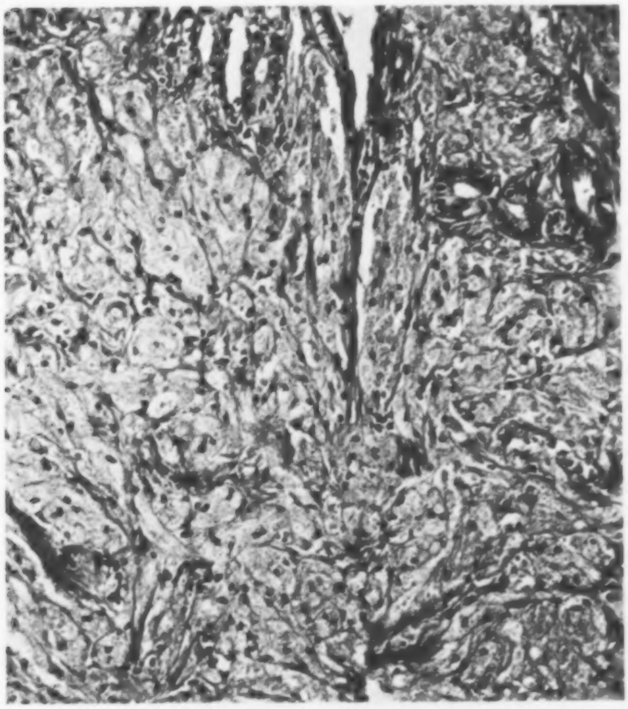

Figure 159
GRANULAR CELL TUMOR
Section shows characteristic granular cells arranged in cords and small nests separated by thin fibrous bands. The epithelium of the cystic duct is seen in the upper part of the photograph. X160.

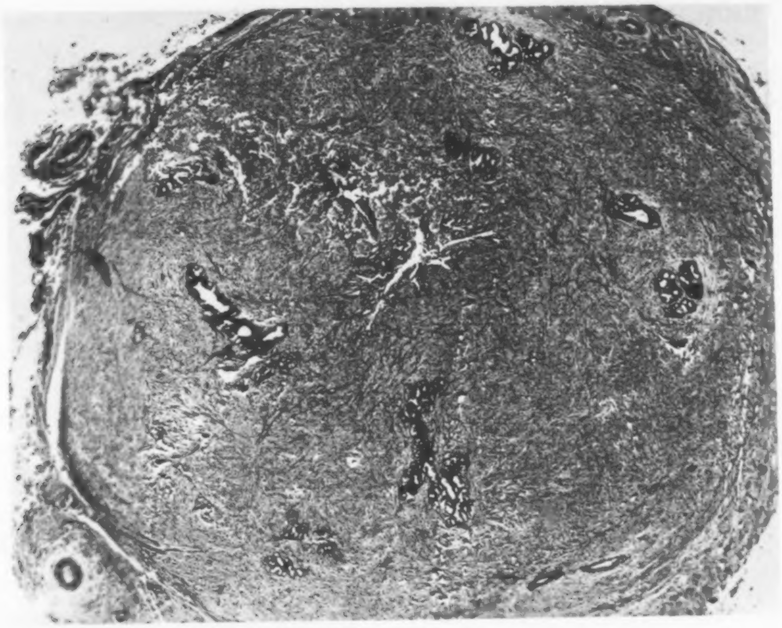

Figure 160
GRANULAR CELL TUMOR
Low power photograph through the cystic duct. The lumen is almost obliterated by a granular cell tumor that has infiltrated the full thickness of the wall. X15.

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PARAGANGLIOMA

A paraganglioma involving the left and right hepatic ducts has been reported. The lesion, which caused obstruction, was successfully removed. It probably arose from the paraganglion cells located in the hilum of the liver.

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BENIGN MESENCHYMAL TUMORS

Benign mesenchymal tumors of the extrahepatic bile ducts are exceptional. Fibromas, lipomas, leiomyomas, and neurilemomas have been described.

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TUMOR-LIKE LESIONS

Tumor-like lesions are occasionally found in the extrahepatic ducts. They primarily include heterotopia and amputation neuromas.

Heterotopia

Heterotopic pancreas and gastric mucosa have been found in the extrahepatic bile ducts. The ectopic tissue can cause obstructive jaundice, especially when located in the ampulla.

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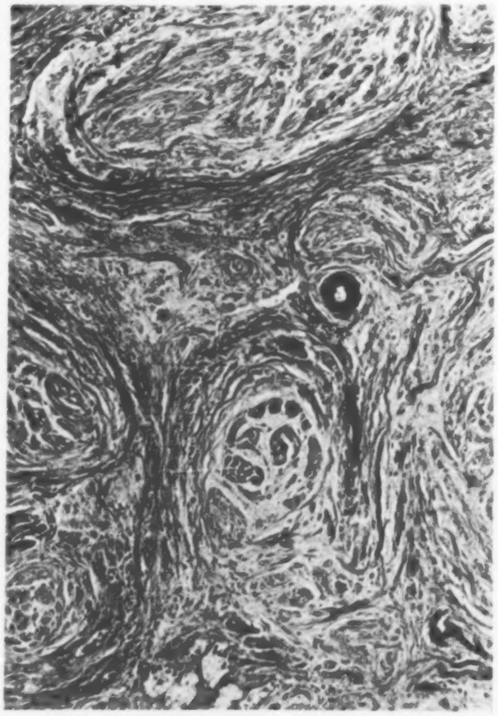

Figure 161
AMPUTATION NEUROMA
Distorted and hypertrophied nerve trunks are separated by fibrous tissue. The lesion was located in the cystic duct stump. X160.

Amputation Neuroma

SYNONYMS AND RELATED TERMS: Traumatic neuroma.

Amputation neuromas, which can occur many years after cholecystectomy, result from the proliferation of transected nerves. Clinically, they are responsible for some cases of post cholecystectomy pain. These neuromas may rarely grow into the lumen of the bile ducts, mimicking a true neoplasm and causing obstructive jaundice (Larson and Storsteen).

Amputation neuromas are most commonly located in the stump of the cystic duct, although other ducts can also be involved following surgery. Grossly, they are nodular and have a gray white whorled cut surface. Histologically similar to neuromas in other sites, they show a conglomeration of distorted nerve fibers supported by variable amounts of fibrous tissue (fig. 161).

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PAPILLOMATOSIS

SYNONYMS AND RELATED TERMS: Papillary adenomatosis; multiple papillary adenomas.

Papillomatosis, or multiple recurring papillary tumors, is extremely uncommon and always attracts special attention. The disease can involve any part of the biliary tree, including the gallbladder and intrahepatic ducts. In some cases, the lesions have included only the intrahepatic ducts (Okulski et al.). In one report, the proximal segment of the pancreatic duct was also affected (Neumann et al.).

Clinically, the disease usually presents as extrahepatic obstructive jaundice. Histologically, it is characterized by multiple papillary lesions which show complex branching and glandular patterns (figs. 162–164). Lesions may appear entirely benign or show focal areas of cellular and nuclear pleomorphism (Madden and Smith). These papillary growths can cover wide areas of the biliary tree and may even extend into the hilum of the liver.

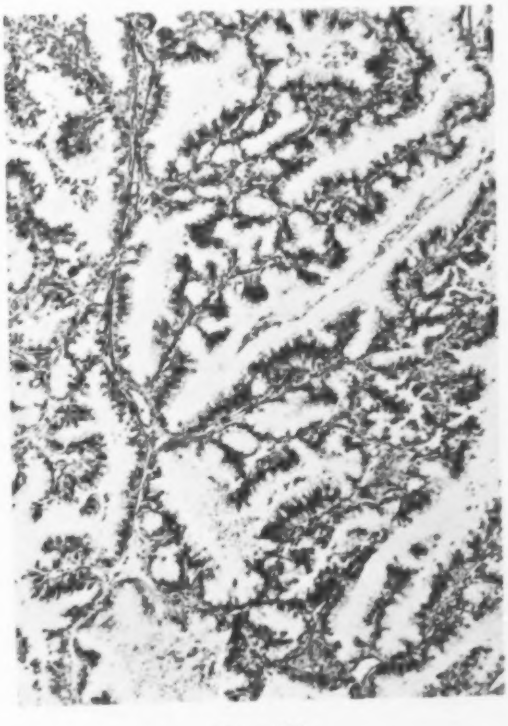

Figure 162
(Figures 162–164 from same patient)
PAPILLOMATOSIS
Numerous long and slender papillary structures lined by columnar epithelium project into the lumen of the common duct. X80.

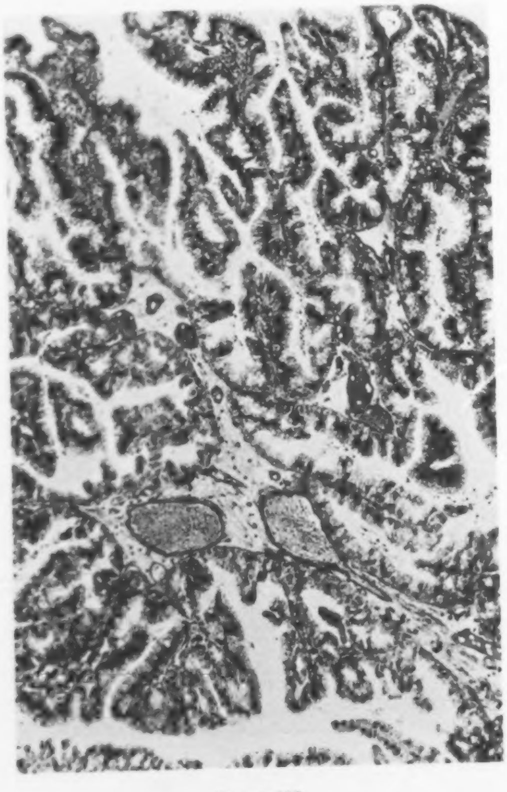

Figure 163
PAPILLOMATOSIS
Another area of tumor shown in figure 162. X80.

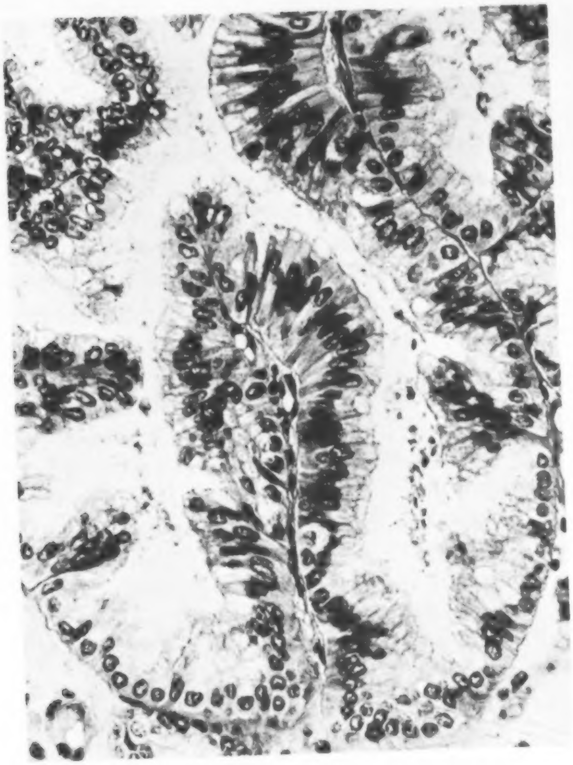

Figure 164
PAPILLOMATOSIS
Closeup of papillary structures shown in figure 163. Epithelial cells have regular basal nuclei and vacuolated cytoplasm. X330.

Because of the high incidence of local recurrence and extensive involvement of the biliary tree, the question of papillary carcinoma often arises with these lesions. Although it is not always possible to exclude malignancy, a lack of invasion into the wall, absence of mitotic figures, and minimal nuclear atypia are helpful in excluding papillary carcinoma.

Papillomatosis is very difficult to treat. Curettage is usually followed by regrowth of the tumor, and often it is not possible to remove all lesions because of location and extent.

Papillary lesions can progress to invasive carcinoma (Helpap; Neumann et al.). For this reason, papillomatosis should be regarded as a precancerous condition.

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MALIGNANT TUMORS OF THE EXTRAHEPATIC BILE DUCTS

Cancer of the extrahepatic bile ducts was possibly described 269 years before carcinoma of the gallbladder, in the year 1508 (Braasch et al.). As with cancer of the gallbladder, over 98 percent are carcinomas. All malignant tumors invariably cause obstruction of the bile ducts and proximal distention. Histologically, the carcinomas are classified in the same manner as the corresponding tumors of the gallbladder.

Cancer of the extrahepatic bile ducts, exclusive of the ampulla, is not as common as cancer of the gallbladder. Among 1808 cases of extrahepatic biliary tract cancer recorded in California, there were 1629 cases of gallbladder cancer, but only 179 of the extrahepatic bile ducts (Krain). In our material there were 386 cancers of the gallbladder and 61 of the bile ducts. Among 56,000 autopsies performed at Los Angeles County Hospital, there were 203 gallbladder cancers and 29 malignant tumors of the extrahepatic ducts (Edmondson). In the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, 1694 cases of gallbladder cancer were recorded from 1973 through 1978, and 912 cases of extrahepatic bile duct cancer.

CARCINOMA OF THE EXTRAHEPATIC BILE DUCTS

Malignant epithelial tumors can arise in any part of the extrahepatic bile ducts. Although these carcinomas are morphologically similar to those in the gallbladder, their incidence, sex distribution, clinical features, association with lithiasis, frequency of histologic types, and treatment are different.

Clinical Manifestations. Carcinoma of the extrahepatic ducts is slightly more common in males in the United States (Table 3). The age of diagnosis has ranged from 23 to over 90 years, and the median age has varied from 59 to 69 years (Warren et al.; fig. 28). Clinically, these tumors usually cause early obstruction that results in jaundice, which can progress or fluctuate. Jaundice usually occurs while the tumor is relatively small and before widespread dissemination. Other symptoms include right upper quadrant pain, malaise, weight loss, pruritus, anorexia, nausea, and vomiting (Bedikian et al.). If cholangitis develops as a complication, chills and fever appear. A palpable mass and ascites usually indicate advanced disease which precludes complete resection of the tumor. As a rule, the liver is enlarged, and if patients survive long enough, it may become nodular because of secondary biliary cirrhosis or metastases. In patients with carcinoma of proximal bile ducts (right and left hepatic ducts, common hepatic duct) the gallbladder is not palpable and the common duct often collapses. Patients with carcinoma in the common or cystic ducts have a distended and palpable gallbladder as well as a markedly dilated proximal duct system.

Less than 20 percent of these tumors are associated with choledocholithiasis. In fact, the association of extrahepatic bile duct carcinoma with gallstones is no greater than expected from the prevalence of gallstones in the general population. We have seen a patient with carcinoma of the cystic duct stump nine years following cholecystectomy. The stump was markedly dilated, resembling a small gallbladder, and, in addition to the carcinoma, contained a single stone.

Laboratory Findings. Laboratory findings reflect obstruction and include increasing levels of serum bilirubin and a rise in alkaline phosphatase. In general, laboratory findings tend to be the same as in carcinoma of the gallbladder. Elevated levels of serum alpha-fetoprotein have been reported in 25 percent of cases (McIntire et al.). The CEA levels in the serum and bile are usually increased.

Radiographic Studies. Cholangiography performed transhepatically or endoscopically usually reveals the site of obstruction and, occasionally, the extent of the lesion (Redeker et al.; Okuda et al.; fig. 165). Ultrasound examination is another important noninvasive procedure in the preoperative diagnosis of these tumors. In fact, sonography is probably the preferred screening procedure for bile duct dilatation. Computed tomography has also proven useful for distinguishing obstructive from nonobstructive jaundice. In a large number of cases it may even clarify the nature of the lesion (Havrilla et al.; Levitt et al.). It seems prudent to consider any noncalculous obstruction in the extrahepatic ducts malignant until proven otherwise, especially in a patient who has not had previous biliary tract surgery (Fortner et al.).

Cytologic Diagnosis. Cytologic examination of duodenal contents or bile collected directly from the common duct has increased the number of cases diagnosed preoperatively. With this method it has been possible to recognize malignant cells in 83 percent of patients (Harada et al.). Use of the percutaneous fine needle aspiration biopsy technic guided by selective angiography or transhepatic cholangiography permits a correct diagnosis of bile duct carcinomas in 50 percent of cases (Evander et al.).

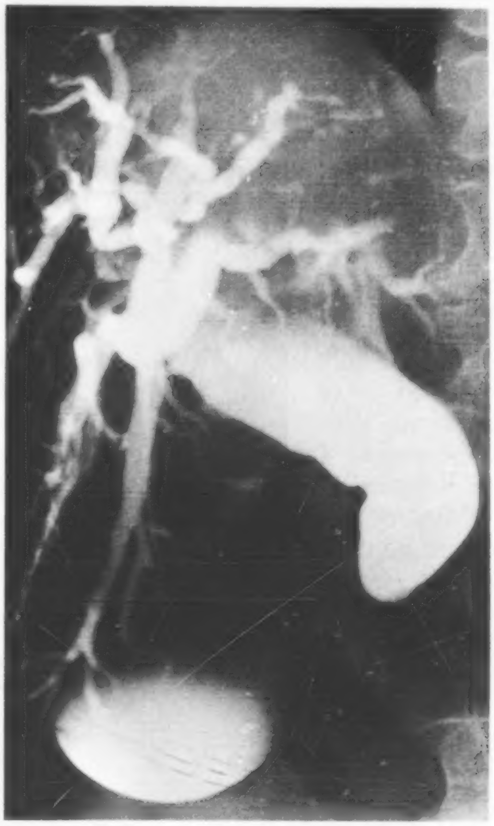


Figure 165
TRANSHEPATIC CHOLANGIOGRAM
Transhepatic cholangiogram showing obstruction and dilatation of the common bile duct that was caused by a well differentiated adenocarcinoma. The fundus of the gallbladder, which is also dilated, is seen. (Courtesy of Dr. A. Rodriguez, Mexico City, Mexico.)

Delay in Diagnosis. About 20 percent of patients with carcinoma of the extrahepatic ducts have had previous surgery without a definitive diagnosis. Unfortunately, additional surgery is often necessary to reach a final diagnosis. In some patients a small carcinoma is overlooked during laparotomy. This is especially true for tumors in the proximal bile ducts, since they are difficult to observe and palpate unless the hilum of the liver is dissected. Sometimes the biopsy is not representative, and a diagnosis of sclerosing cholangitis is made. On occasion, when cholecystectomy for lithiasis is performed, the neoplasm is mistaken for a fibrous scar and a biopsy is not obtained. In summary, a diagnosis is often established late and usually during laparotomy. Reasons for the delay include lack of an obvious tumor or confusion with lithiasis, fibrous stricture, or primary sclerosing cholangitis (Wanebo and Grimes).

Anatomic Distribution. For prognostic and therapeutic purposes it is useful to divide the extrahepatic ductal system into three parts — upper, middle, and lower thirds. Almost 50 percent of all carcinomas are located in the upper third, 25 percent in the middle third, and 19 percent in the lower third (Tompkins et al.). In less than 10 percent, it is not possible to specify the origin because of diffuse involvement of the bile ducts (Diagram 1).

Gross Features. These tumors usually appear as small infiltrating nodular and constricting lesions or as polypoid indurated masses (figs. 166, 167). A combination of these two features is often seen. On occasion, there is only a thickening or induration of the wall of the bile duct, which otherwise shows only a roughened and granular mucosa. These changes can easily be overlooked on macroscopic examination by surgeons and pathologists. Invariably, mucosal ulceration and obstruction occur. Most bile duct carcinomas are gray white,

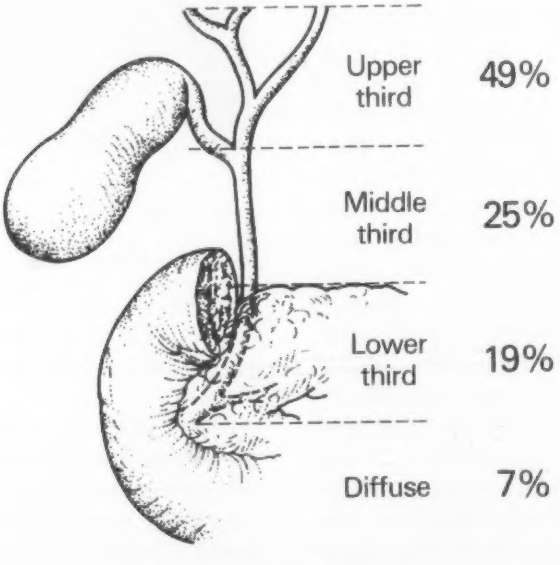


DIAGRAM 1
CARCINOMA OF THE BILE DUCTS
Anatomic distribution of malignant tumors in the extrahepatic bile ducts. (Modified from Tompkins, R.K., Thomas, D., Wile, A., and Longmire, W.P., Jr. Prognostic factors in bile duct carcinoma. Ann. Surg. 194:447-455, 1981.)

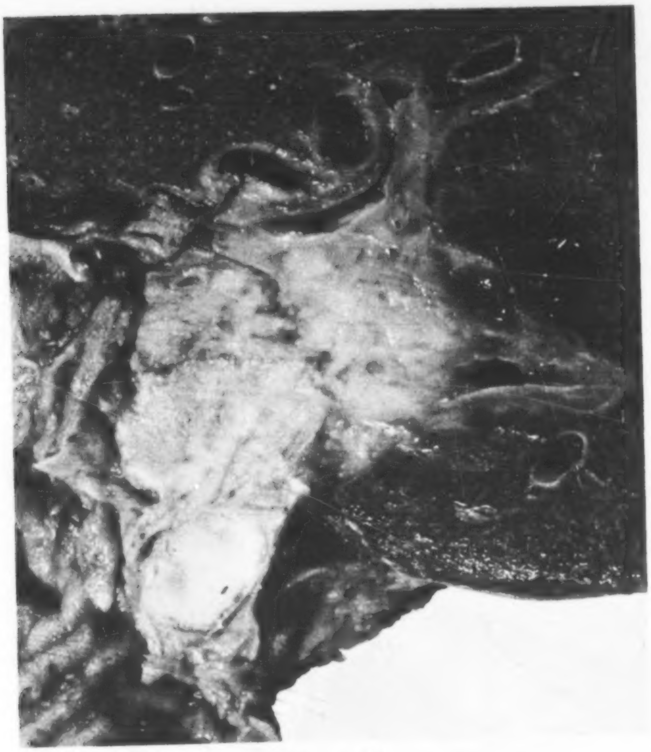
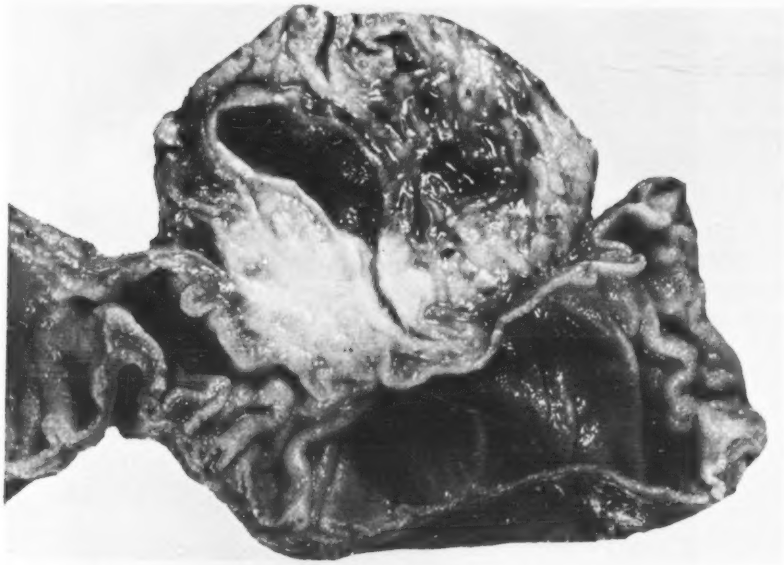


Figure 166
CARCINOMA OF THE COMMON HEPATIC DUCT
The tumor, which arose in the common hepatic duct, has extended along the right and left hepatic ducts into the hilum of the liver. A lymph node replaced by metastatic tumor is visible.

firm, and not well defined. A few are friable and necrotic, especially pleomorphic giant cell and oat cell carcinomas. Colloid carcinomas have a gelatinous appearance. Extensive necrosis, however, is not common. Despite the small size of most tumors, by the time of diagnosis they have usually spread to adjacent tissues and about one-third have regional lymph node metastases (pl. IV-B). If the tumor has spread along the entire biliary duct system, it may not be possible to determine the origin.

Grossly, tumors of the hepatic ducts can be separated into polypoid, nodular, scirrhous constricting, or diffusely infiltrating types (Todoroki et al.). This separation is important for the surgeon, because it often provides a guide to the operative procedure, extent of resection, and prognosis. However, except for the polypoid tumors, this separation is rarely possible in practice because of overlapping gross features. As in the gallbladder, polypoid tumors, which usually prove to be papillary carcinomas histologically, have the best prognosis. The nodular and scirrhous types tend to infiltrate surrounding tissues and are difficult to resect. The diffusely infiltrating types tend to spread linearly along the ducts.



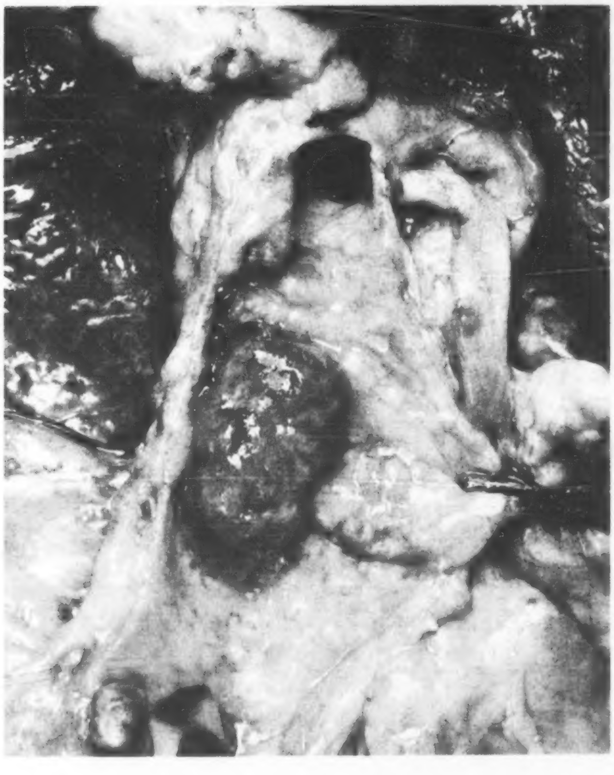


Figure 167
CARCINOMA OF THE
COMMON BILE DUCT

(A) This infiltrating gray white mass that arose in the distal part of the common bile duct has invaded the pancreas and wall of the duodenum. The proximal part of the common duct is greatly dilated.

(B) This polypoid carcinoma had obstructed the common bile duct and infiltrated its circumference. (Fig. 167B is fig. 97 from Fascicle 26, First Series.)

Microscopic Description. The microscopic features of these tumors do not differ from those found in the gallbladder and for this reason will not be described in detail. However, some differences should be noted. The proportion of well differentiated adenocarcinomas in the extrahepatic ducts is higher than in the gallbladder. In our 61 patients, 81 percent were well differentiated adenocarcinomas (Table 6). In contrast, the incidence of other types, especially pleomorphic giant cell carcinomas and oat cell carcinomas, is lower in the bile ducts. Recently, we have seen one case of an intestinal-type carcinoma of the cystic duct that was not associated with intestinal metaplasia of the adjacent mucosa.

Table 6

HISTOLOGIC TYPES IN 61 PATIENTS WITH EXTRAHEPATIC BILE DUCT CARCINOMAS

Histologic Type	Number of Patients	Percentage
Adenocarcinoma, well differentiated	50	81.8
Pleomorphic giant cell adenocarcinoma	4	6.5
Adenosquamous carcinoma	4	6.5
Oat cell carcinoma	2	3.2
Colloid carcinoma	1	1.6
Total	61	99.6

As a group, tumors arising in the proximal segment of the extrahepatic ducts tend to be better differentiated. The stroma is more sclerotic and usually contains chronic inflammatory cells. Consequently, these tumors are more apt to be confused with sclerosing cholangitis than the less differentiated tumors that arise more distally (figs. 168–180). A few papillary adenocarcinomas, squamous cell carcinomas, and adenosquamous carcinomas have also been reported in this proximal location (Aranha et al.; figs. 181, 182), but not pleomorphic giant cell carcinomas nor oat cell carcinomas. In fact, in our material, these two types were found only in the common duct (figs. 183, 184).

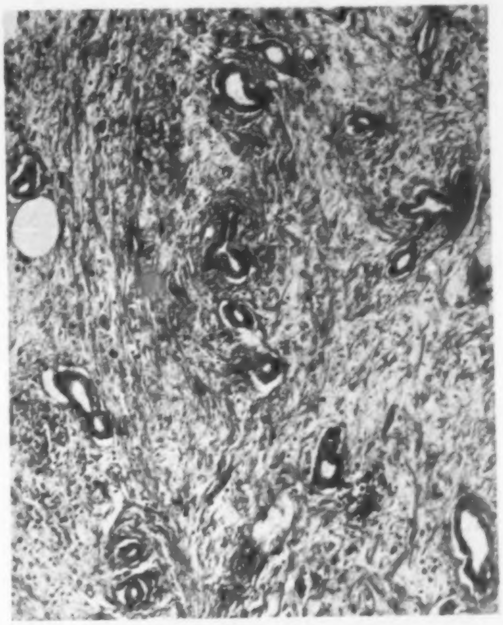


Figure 168

WELL DIFFERENTIATED ADENOCARCINOMA

A well differentiated adenocarcinoma in the right hepatic duct. Small tubular glands lie in an abundant fibrous stroma which contains some chronic inflammatory cells. This tumor may be difficult to distinguish from chronic sclerosing cholangitis. X80.

As in the gallbladder, papillary carcinomas grow toward the lumen before they invade the wall (fig. 179). In contrast, pleomorphic giant cell carcinomas rapidly extend to adjacent structures.

All carcinomas that we have studied by immunocytochemistry contain CEA. The

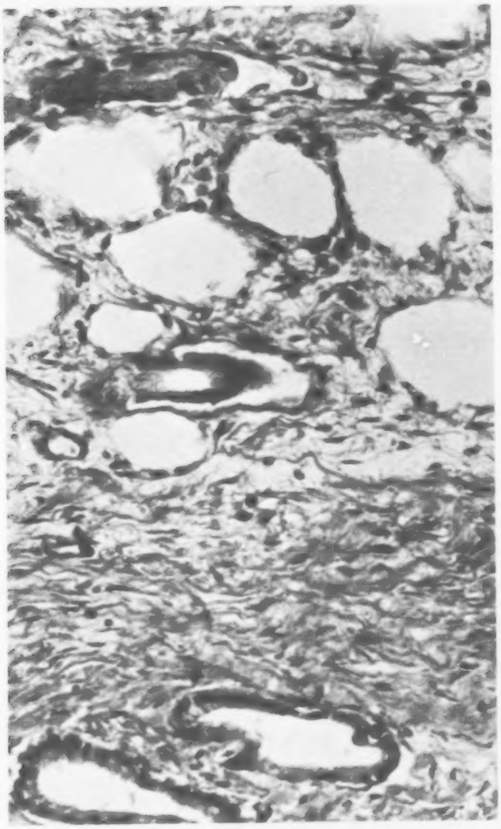


Figure 169
WELL DIFFERENTIATED ADENOCARCINOMA
Small tubular glands have infiltrated the periductal fibrous and adipose tissue. X160.

antigen is also found in dysplastic lesions and in carcinomas in situ. In normal bile duct epithelium, CEA is seen only along the apical cytoplasm of a few epithelial cells.

Perineural invasion is seen in almost every case that is adequately sampled and should be specifically evaluated, since it allows separation from primary sclerosing cholangitis (fig. 185).

Differential Diagnosis. Problems in the differential diagnosis are more common than with gallbladder cancer. They usually result from local extension of the tumor and obliteration of its primary site.

Carcinomas of the extrahepatic ducts can extend to the liver, pancreas, ampulla, duodenum, or gallbladder. Since all of these organs give rise to malignant epithelial neoplasms similar to those originating in the biliary ducts, identification of their exact origin may be difficult, especially with large cancers. Histologic examination alone is often of little help in the differential diagnosis unless carcinoma in situ or severe dysplasia is found in the mucosa adjacent to the bile duct carcinoma. In our material this was not helpful, since we found these precursor lesions in only 10 percent of patients. In many patients, the diagnosis can only be reached after careful clinicopathologic correlation, including a review of the radiographic and operative findings. Also, the pathologist should recall that the clinical presentation and biologic behavior vary according to the origin of the tumor. For example, carcinomas of the pancreas tend to metastasize more widely than carcinomas of the bile ducts or of the ampulla. Cholangiography and computed tomography have helped clinicians locate the primary tumor even when small and localized. Grossly, the bulk of the tumor is found at the site of origin.

Nevertheless, in some cases it may not be possible to specify with certainty the origin of the tumor. This uncertainty has led to the use of nonspecific terms such as carcinoma of the periampullary region (Wise et al.) or hilar carcinoma of the liver (Okuda et al.), which reflect the difficulties involved in locating the primary site.

The differentiation of extrahepatic bile duct carcinoma from sclerosing cholangitis is discussed on page 194.

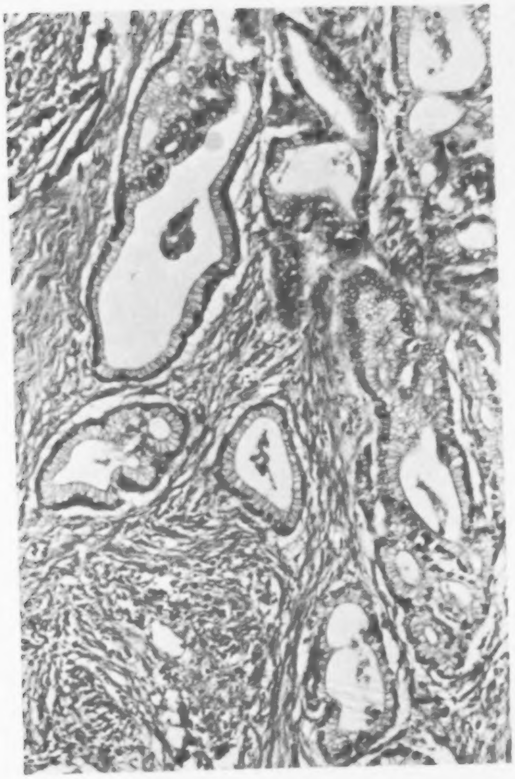


Figure 170
(Figures 170 and 171 from same patient)
WELL DIFFERENTIATED ADENOCARCINOMA
A well differentiated adenocarcinoma of left hepatic duct, showing different size glands. X125.

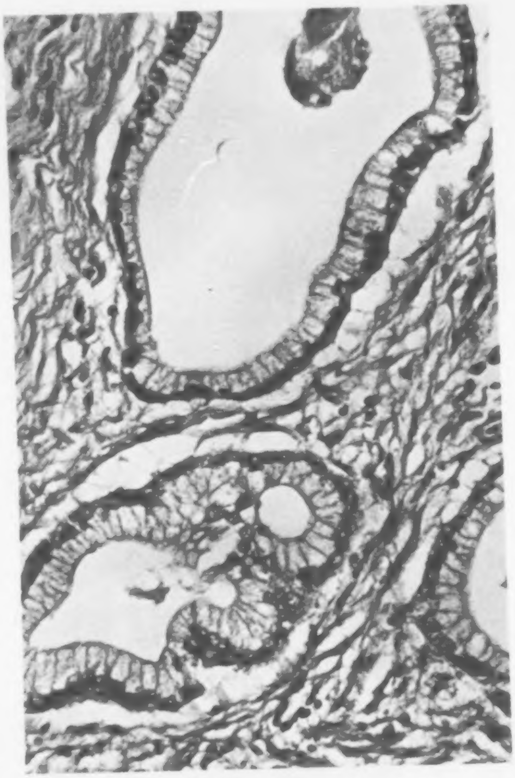


Figure 171
WELL DIFFERENTIATED ADENOCARCINOMA
Higher magnification of tumor shown in figure 170. The glands are lined by tall columnar mucus-secreting cells with basal nuclei and surrounded by a dense fibrous stroma. X180.

Spread and Metastasis. These tumors usually spread early to adjacent tissues by local extension. Direct extension initially occurs to the periductal connective tissue and surrounding nerves. Local spread through the wall of the bile ducts is commonly encountered, the ducts often being transformed into rigid tubes. Carcinomas arising in the left or right hepatic ducts may either extend proximal to the liver or distal to the common hepatic duct. Neoplasms from the cystic duct tend to invade the neck of the gallbladder or common bile duct. Carcinomas arising in the distal third of the common bile duct usually extend to the pancreas or duodenum, but rarely to the stomach or colon. Metastases have been reported in 30 to 70 percent of cases. Regional lymph nodes and liver are the most common sites for metastasis. Hematogenous metastases are uncommon and usually occur late. Diffuse peritoneal seeding is also a late manifestation.

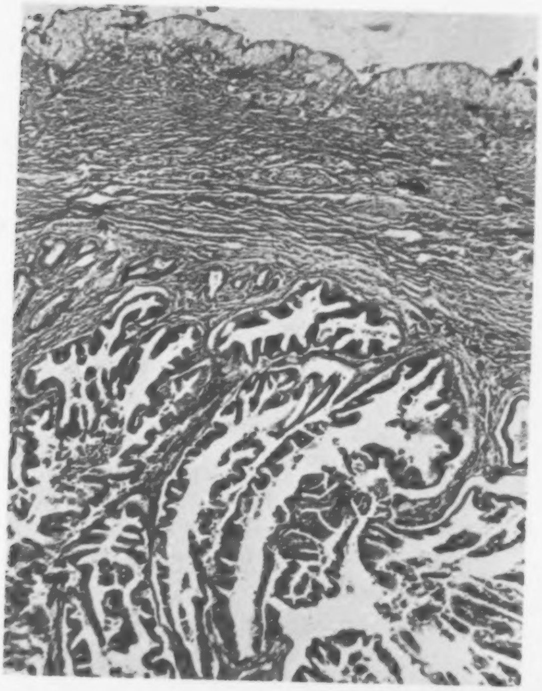


Figure 172
WELL DIFFERENTIATED ADENOCARCINOMA

This tumor, which arose in the common duct, is composed of long tubular branching glands. The glandular structures are in marked contrast to the small glands shown in figure 168. The duct also shows mild cholesterolosis characterized by foamy histiocytes in the subepithelial layer. X100.

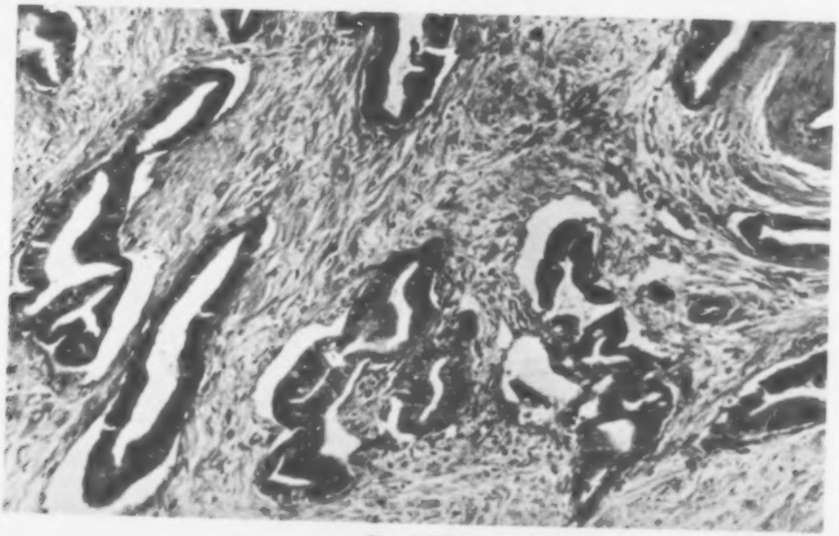


Figure 173
WELL DIFFERENTIATED ADENOCARCINOMA

Well differentiated adenocarcinoma of the common bile duct. This tumor is composed of medium size glands lined by tall columnar cells that are less mucus-secreting than shown in Figure 171. X125.

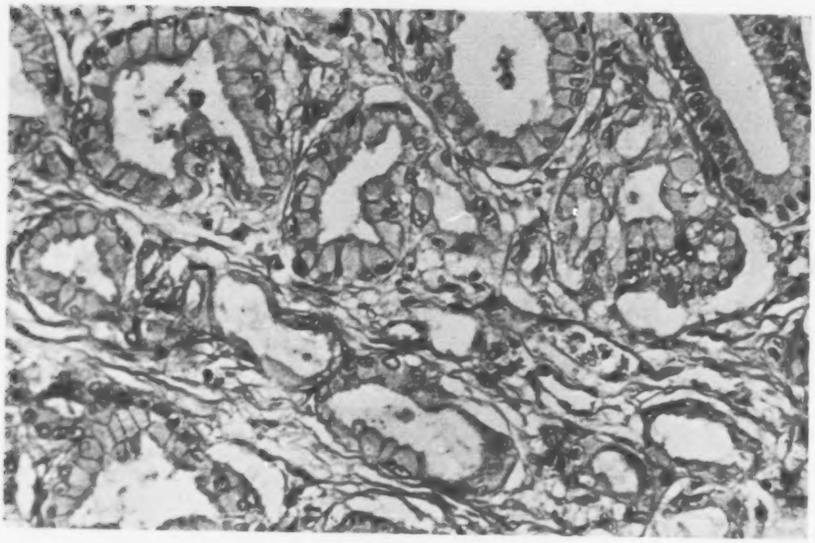


Figure 174
WELL DIFFERENTIATED ADENOCARCINOMA
In this tumor, which arose in the hilum, the glandular structures are lined by tall columnar mucus-secreting cells and separated by a small amount of fibrous stroma. In the upper right corner, there is a normal bile duct. X160.

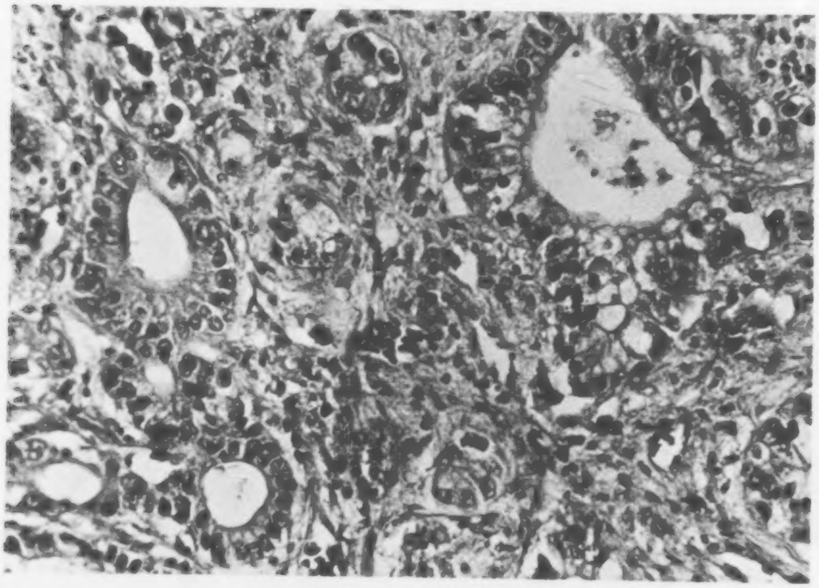


Figure 175
WELL DIFFERENTIATED ADENOCARCINOMA
In some tumors there may be more nuclear pleomorphism. X200.

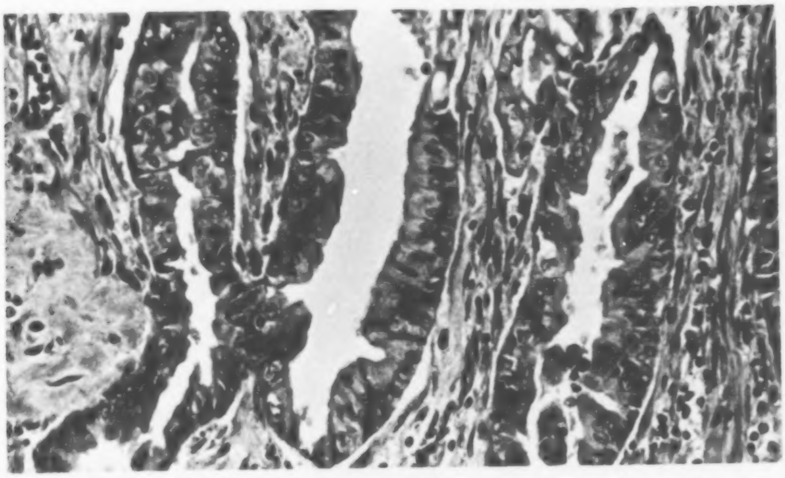


Figure 176
WELL DIFFERENTIATED ADENOCARCINOMA
Branching tubular glands in a well differentiated adenocarcinoma that arose in the common bile duct. X200.

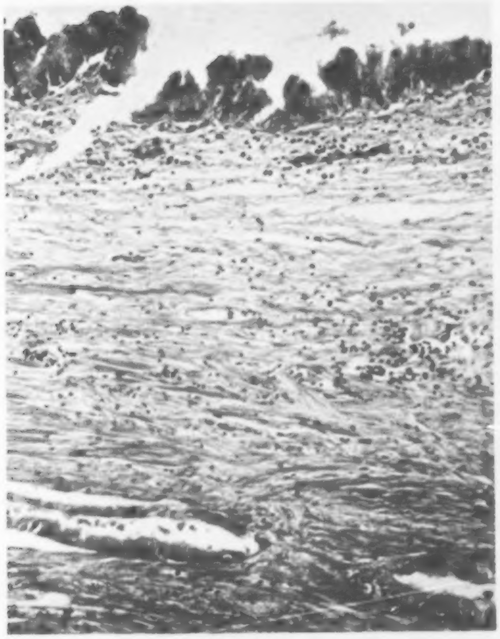


Figure 177
WELL DIFFERENTIATED ADENOCARCINOMA
Tumor that arose in the common duct shows long tubular glands in the wall and carcinoma in situ along the surface. X150.

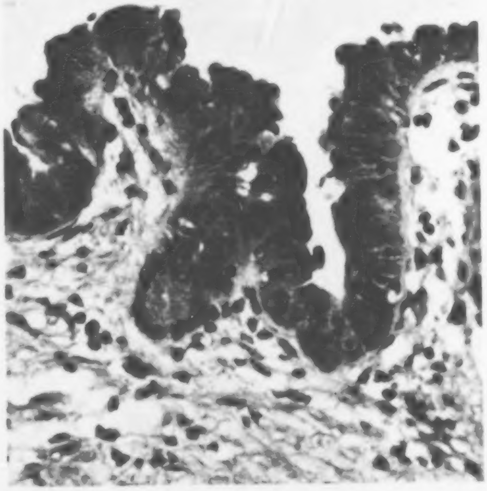
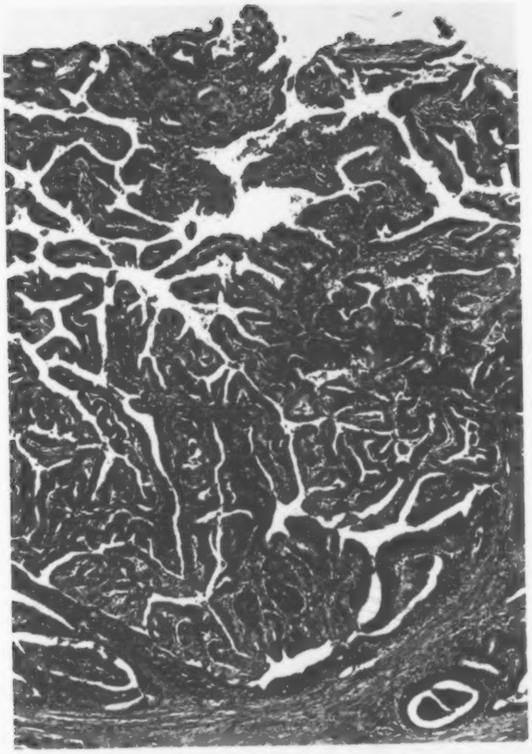


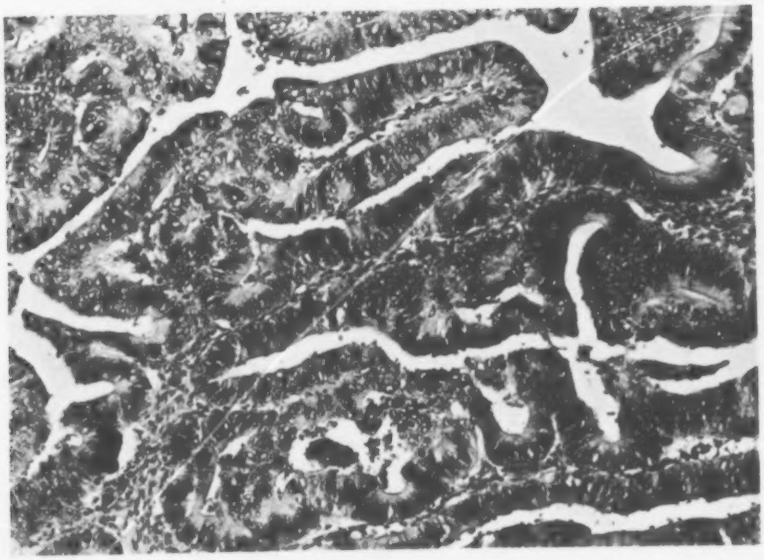
Figure 178
CARCINOMA IN SITU
OF COMMON HEPATIC DUCT
Carcinoma in situ adjacent to an infiltrating carcinoma of common hepatic duct. The normal epithelium of the duct has been replaced by hyperchromatic neoplastic cells that are columnar in shape and pseudostratified. X330.



A

Figure 179
PAPILLARY CARCINOMA

(A) This papillary carcinoma, which has grown into the lumen of the common bile duct, shows several small foci of invasion. X38. (B) Higher magnification of the same tumor, showing papillary structures lined by tall columnar neoplastic cells. X130. (Courtesy Dr. Sharon Thompsen, Miami, FL.)



B

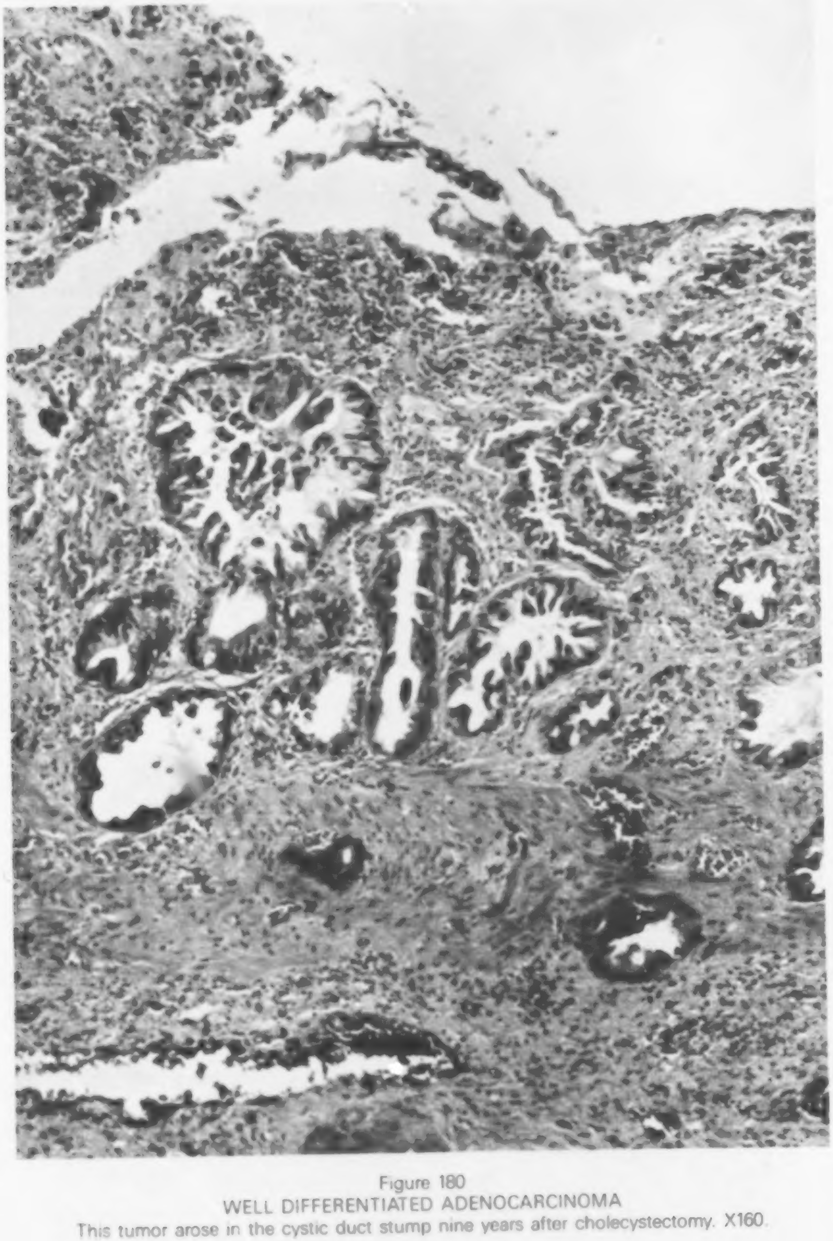


Figure 180
WELL DIFFERENTIATED ADENOCARCINOMA
This tumor arose in the cystic duct stump nine years after cholecystectomy. X160.

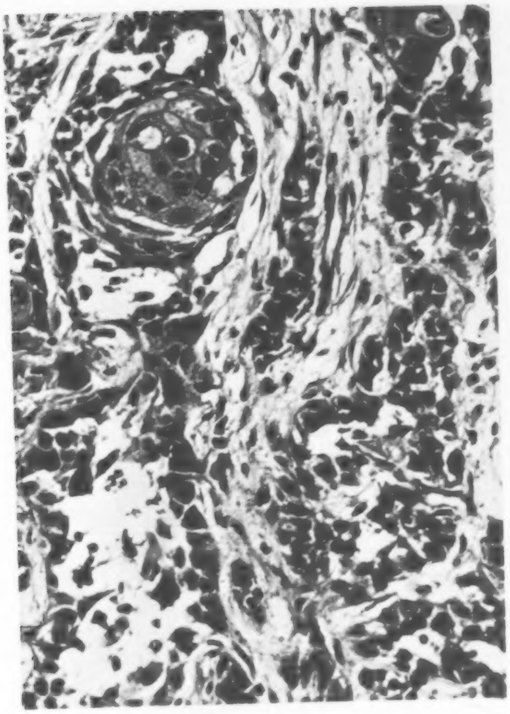


Figure 181
ADENOSQUAMOUS CARCINOMA
OF COMMON BILE DUCT

Poorly defined glandular structures lined by cuboidal cells and nests of squamous cells are seen in the adenosquamous carcinoma of the distal third of the common bile duct. X200.

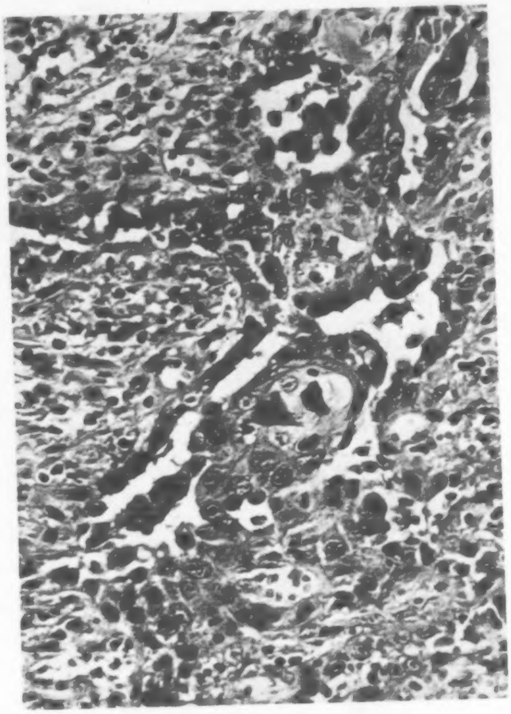


Figure 182
ADENOSQUAMOUS CARCINOMA
OF COMMON BILE DUCT

A branching gland contains a nest of neoplastic squamous cells. The stroma is infiltrated by chronic inflammatory cells. X200.

Treatment and Prognosis. Despite the fact that most of these tumors are generally small, well differentiated, and tend to remain localized, the results of surgical treatment have been disappointing. Of 221 patients, only 8 (3.6 percent) survived five years or longer (Adson and Farnell). The best results are observed in patients with tumors in the distal third of the common duct in whom a pancreatoduodenectomy is possible (Longmire et al.). The five-year survival rate in this group is 28 percent (Tompkins et al.). Tumors of the middle part of the common bile duct are usually treated by local excision with anastomosis of the proximal duct to the intestine. Of 24 patients with tumors in this region, only 3 (12.5 percent) survived five years (Tompkins et al.).

Patients with lesions in the proximal ductal system are the most difficult to treat and often require major hepatic resections (Iwasaki et al.). In a series of 80 patients with hilar tumors, only four tumors could

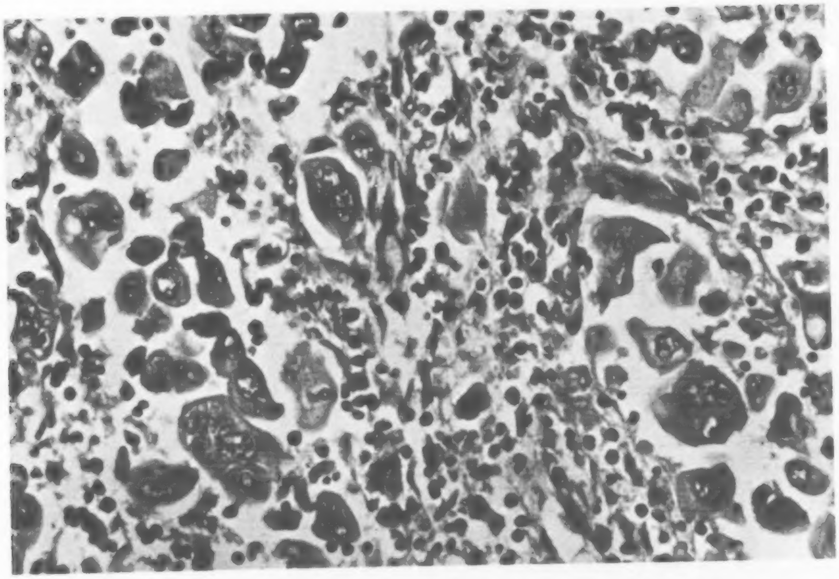


Figure 183
PLEOMORPHIC GIANT CELL ADENOCARCINOMA
OF COMMON BILE DUCT

Pleomorphic large cells with no cohesion form most of this tumor in the common bile duct. This type of common duct tumor is histologically similar to those arising in the gallbladder. X300.

be resected (Bismuth and Corlette). Of 47 patients with carcinomas of the upper third of the extrahepatic ductal system treated surgically, none survived five years (Tompkins et al.). Since these are slow growing malignant tumors, palliative treatment that re-establishes biliary flow is indicated. Some patients have survived several years following such a procedure (Klatskin). Death often results from biliary obstruction, liver failure, and ascending cholangitis.

Several reports indicate that radiotherapy increases survival, although these studies were not randomized (Hanna and Rider; Koperson and Gunderson). Liver transplantation has also been tried in the treatment of extrahepatic bile duct carcinomas, but with no success.

The staging system developed for extrahepatic bile duct cancer, exclusive of the ampulla, by the American Joint Committee on Cancer is as follows (Beahrs and Myers):

T_{is}	In situ carcinoma
T1	Invasion limited to wall
T2	Invasion limited to periductal connective tissues.
T3	Involvement of all layers of wall and direct extension into one adjacent major vessel or organ.
T4	Involvement of all layers of wall and direct extension beyond secondary ductal bifurcation or into two or more adjacent organs including: liver, pancreas, duodenum, stomach, colon, omentum, and gallbladder.

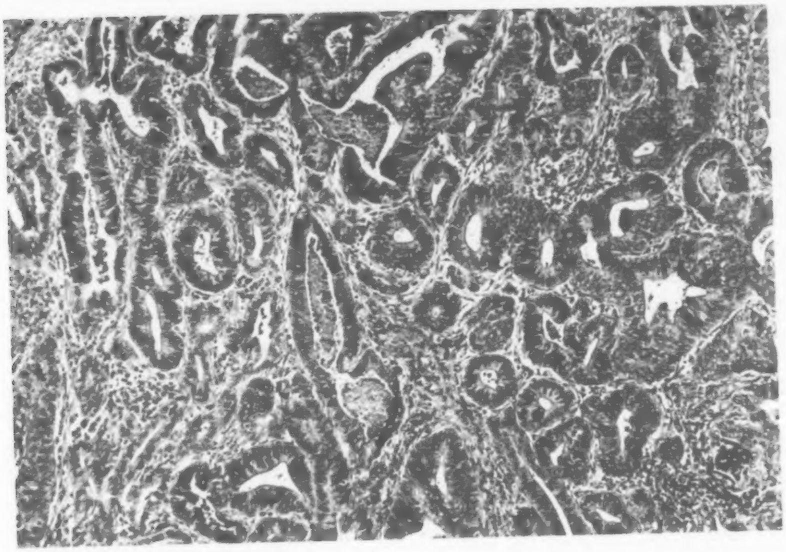


Figure 184(A)
INTESTINAL-TYPE CARCINOMA OF CYSTIC DUCT
This cystic duct tumor closely resembles the adenocarcinomas that arise in the colon. This is an unusual morphologic variant of adenocarcinomas of the extrahepatic bile ducts. A similar tumor is also found in the gallbladder. X80.

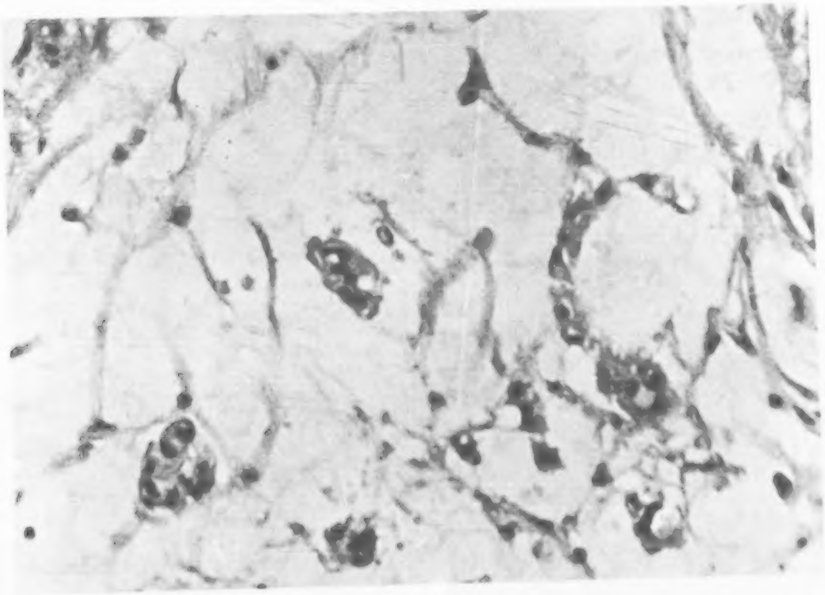


Figure 184(B)
COLLOID CARCINOMA OF COMMON BILE DUCT
Pools of mucin contain small clusters of malignant epithelial cells. Tumor originated in the common bile duct. X200.

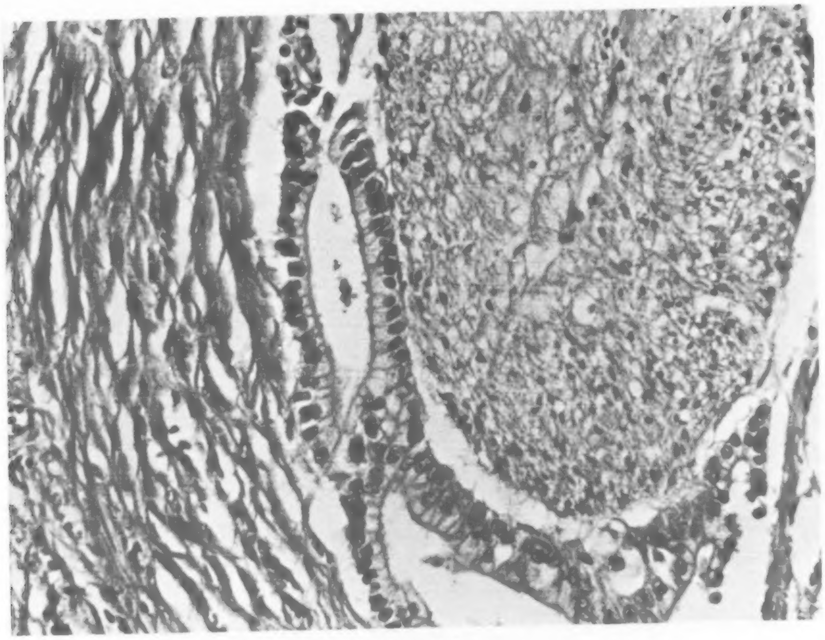


Figure 185
PERINEURAL INVASION
Perineural invasion by a well differentiated adenocarcinoma arising in the common bile duct. The prominent periductal nerve trunks are nearly always invaded. X200.

Periampullary Tumors

Tumors arising in the head of the pancreas, second part of the duodenum, ampulla, or terminal portion of the common duct can obstruct the bile duct, causing symptoms similar to those tumors occurring more proximally. By the time of surgery, it is usually not possible to determine the primary site; thus these tumors are collectively referred to as ampullary tumors. They are discussed in the Fascicle on Tumors of the Pancreas.

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CARCINOMA IN CHOLEDOCHAL CYST

Choledochal cyst, or congenital cystic dilatation, is the second most common anomaly of the extrahepatic biliary tract. It can involve any part of the biliary tree, including the intrahepatic ducts as well as the intraduodenal segment of the common duct (Arthur and Stewart; Longmire et al.). These congenital cysts, which are found in all age groups, can become quite large, often measuring up to 15 cm in diameter. Most cases, however, are recognized in the first two decades of life, usually as a result of an abdominal mass, pain, and bile duct obstruction. The cysts probably result from a congenital defect in the wall of the bile duct. They seem to be more prevalent in Orientals than in Caucasians, judging from the number of reported cases.

Based on the location and structure of the cyst, several classification schemes of pathologic and surgical importance have been proposed. The following classification includes five major types (Todani et al.). Type I involves the hepatic or common bile ducts in a localized, segmental, or diffuse manner. It is the most common type and the one best known by surgeons and pathologists. Type II is a diverticulum-type cyst located along any part of the extrahepatic bile ducts. Type III, which is a choledochocele, occurs in the intraduodenal segment of the common duct. It is often considered an enterogenous cyst. Type IV consists of multiple cysts along the extrahepatic or both the intrahepatic and extrahepatic ducts. Type V is an intrahepatic ductal cyst, either single or multiple. Cystic dilatation of the intrahepatic bile ducts is also known as Caroli's disease.

An association between choledochal cysts and carcinoma is well established (Flanigan; Bloustein). Carcinomas usually arise from these cysts several years after the establishment of internal drainage, usually via a choledochocystoduodenostomy or choledochocystojejunostomy. Consequently, the treatment of choice is excision of the cyst. The average age of patients who develop carcinoma is 37 years, which is considerably below the average of patients with carcinoma of the biliary tree in the absence of cysts. It has been estimated that 2.5 to 15 percent of patients with choledochal cysts will develop carcinoma. Stones are present in 25 percent of cysts with carcinoma. Choledochal cysts can occur in association with congenital hepatic fibrosis (Lake et al.; Fujiwara et al.)

The cyst wall is composed of dense fibrous connective tissue which may be devoid of all epithelial lining and usually contains inflammatory cells (figs. 186, 187). Because of its location, the choledochocele is lined by duodenal mucosa inside and out. Adenocarcinoma is the most common malignant tumor complicating biliary cysts;

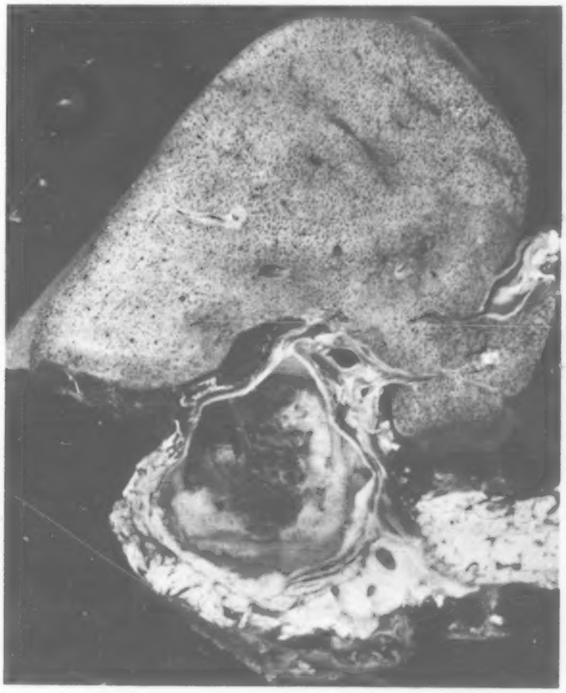

Figure 186
(Figures 186 and 187 from same patient)
CARCINOMA IN CHOLEDOCHAL CYST
Photograph of a cystic dilatation of the common bile duct, in which a squamous cell carcinoma arose and involved only part of the lining. (Fig. 100 from Fascicle 26, First Series.)

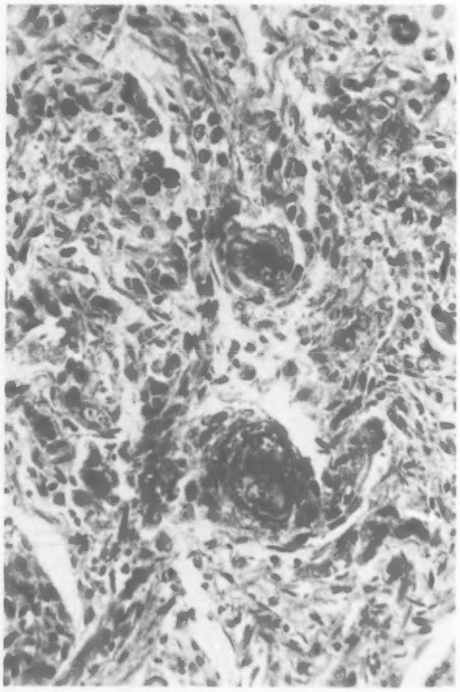

Figure 187
SQUAMOUS CELL CARCINOMA
IN CHOLEDOCHAL CYST
Histologic section of the squamous cell carcinoma that had infiltrated the wall of a choledochal cyst. Note the pearl formation. X160. (Fig. 101 from Fascicle 26, First Series.)

although squamous cell carcinomas, adenosquamous carcinomas, giant cell adenocarcinomas, and even an embryonal rhabdomyosarcoma have been reported. The most common site for the tumor is the posterior wall of the cyst. Tumors most commonly arise in cysts classified as types I and IV and are uncommon in types II, III, and V (Todani et al.). Severe or fatal peritonitis can result from rupture of a cyst.

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CARCINOSARCOMAS

Carcinosarcomas can also occur in the extrahepatic bile ducts. They are more common in the gallbladder, however.

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MALIGNANT MESENCHYMAL TUMORS

Malignant mesenchymal tumors of the extrahepatic ducts are extremely unusual, especially in adults. A review of 912 cases of extrahepatic bile duct cancer, collected by the National Cancer Institute, revealed only one example – a case of malignant fibrous histiocytoma. Because these tumors are unusual, very little information is available on treatment and prognosis. The most important member of this group is a type of rhabdomyosarcoma traditionally known as sarcoma botryoides.

Embryonal Rhabdomyosarcoma

Embryonal rhabdomyosarcoma (sarcoma botryoides) is the most common neoplasm of the biliary tree in childhood (Davis et al.). It may arise from any extrahepatic bile duct, but the common duct is most often the site of origin. The tumor usually extends by submucosal growth along the remaining biliary tree, including the gallbladder and intrahepatic ducts, eventually causing obstruction (Lack et al.).

Grossly, it consists of soft and confluent polypoid structures that often have a characteristic grapelike appearance. Histologically, the polypoid structures are covered with a single layer of epithelial cells continuous with those of the bile ducts (fig. 188). Immediately beneath the epithelium is a concentration of primitive mesenchymal cells with hyperchromatic nuclei and little cytoplasm. This concentration is often referred to as the cambium layer and is also found in embryonal rhabdomyosarcomas that arise in other hollow viscera (fig. 189). The central portion usually contains stellate cells loosely arranged in a myxomatous

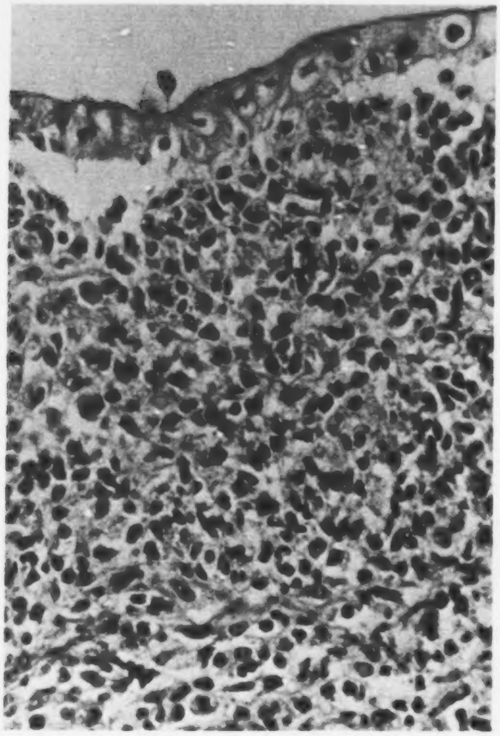

Figure 188
RHABDOMYOSARCOMA
OF COMMON BILE DUCT
Section from the surface of a tumor. It shows the cuboidal epithelium and dense subepithelial concentration of primitive mesenchymal cells. X300. (Courtesy of Dr. E. Lopez-Corella, Mexico City, Mexico.)

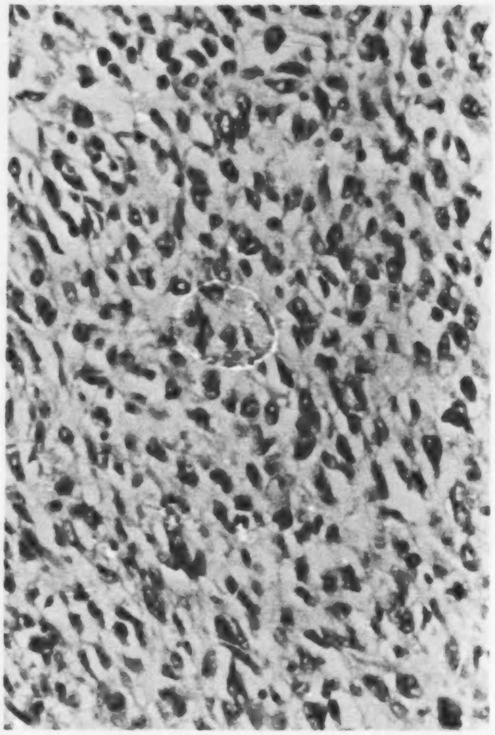

Figure 189
RHABDOMYOSARCOMA
OF COMMON BILE DUCT
In the deeper areas, the tumor can consist of malignant mesenchymal cells that show no particular differentiation. X250. (Courtesy of Dr. E. Lopez-Corella, Mexico City, Mexico.)

matrix. In some areas, but especially in the cambium layer, the tumor cells often have a globular eosinophilic cytoplasm (fig. 190). These globular cells are malignant rhabdomyoblasts and may contain cross striations which are best demonstrated by phosphotungstic acid hematoxylin (PTAH) or Masson trichrome stains (pl. IV-C). About one-third of these tumors have cells with cross striations visible by light microscopy, although these structures are not necessary to establish the diagnosis (fig. 191). With immunohistologic technics, we have detected actin, myosin, and myoglobin in these cells.

In cells without visible cross striations in the light microscope, electron microscopy frequently reveals thin and thick filaments often arranged in a sarcomere-like pattern (Kindblom and Dalberg).

Almost all patients die shortly after diagnosis from local extension and less often from distant metastases. The few survivors that have been reported were treated with radical surgery, irradiation, and chemotherapy (Akers and Needham).

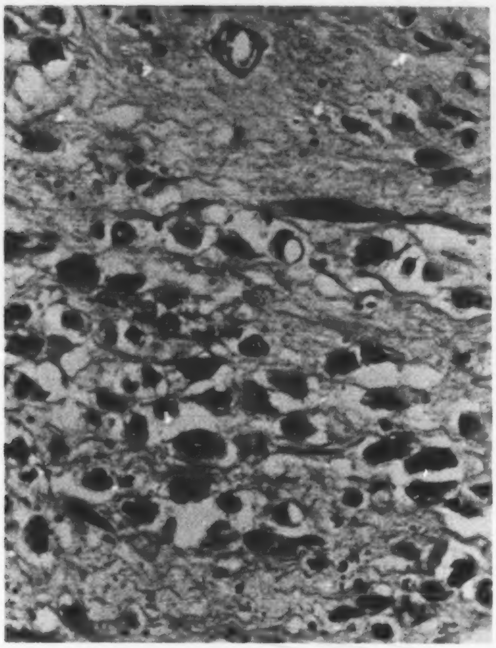

Figure 190
RHABDOMYOSARCOMA
OF COMMON BILE DUCT
In another rhabdomyosarcoma, the tumor consisted of scattered globular and strap cells that characterize rhabdomyosarcomas. X350.

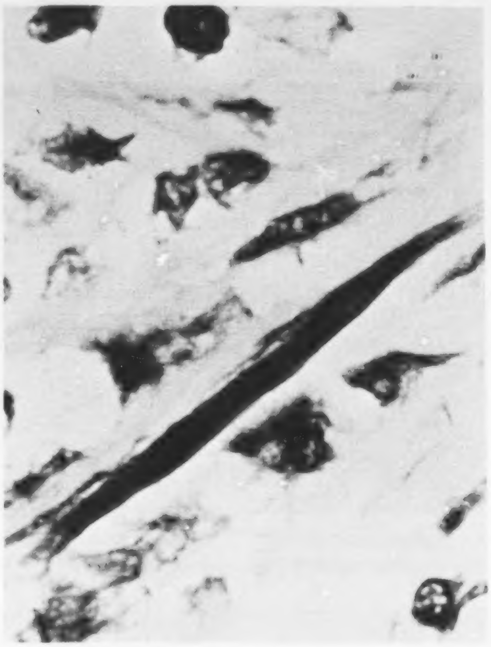

Figure 191
RHABDOMYOSARCOMA
OF COMMON BILE DUCT
A differentiated striated muscle cell is seen. X1100.

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Leiomyosarcoma

Even though smooth muscle is normally present in the wall of the extrahepatic ducts, leiomyosarcomas are unusual in this location. We have been able to locate only three reported cases, one of which occurred in the ampulla.

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PLATE IV

A. EMBRYONAL RHABDOMYOSARCOMA

Embryonal rhabdomyosarcoma of gallbladder. Globular rhabdomyoblasts contain myosin. PAP. X160.

B. ADENOCARCINOMA

Adenocarcinoma of the right hepatic duct, which extended to the bifurcation and periductal connective tissue. The rubber tube is in the left hepatic duct.

C. EMBRYONAL RHABDOMYOSARCOMA

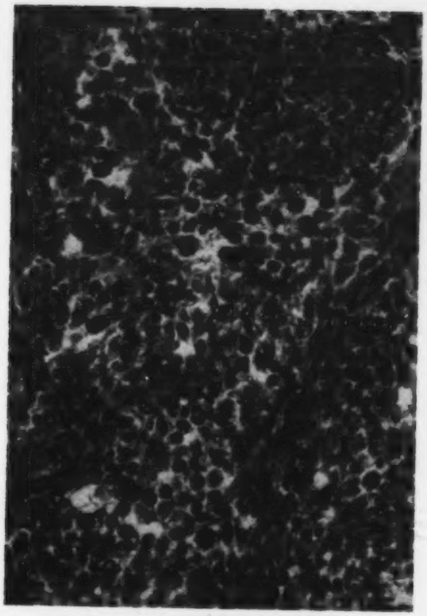
Embryonal rhabdomyosarcoma of common bile duct. Strap shaped malignant rhabdomyoblasts have abundant cytoplasm, which stains deep red. Masson trichrome stain. X500.

D. D CELL CARCINOMA

(Plate IV-D and figure 195 from same patient)

Nearly all cells of this D cell carcinoma of the cystic duct stain for somatostatin. PAP somatostatin antibody. X400.

PLATE IV



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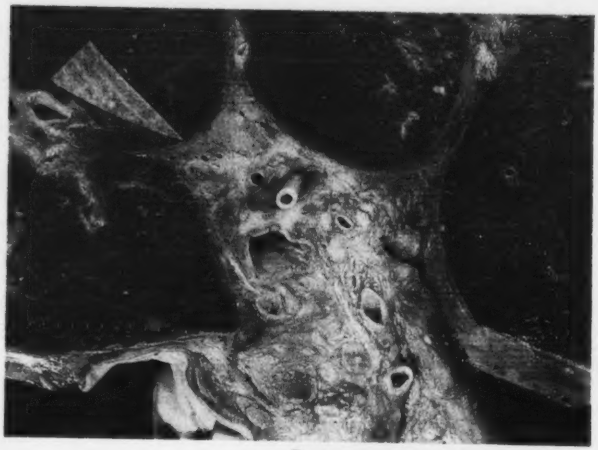

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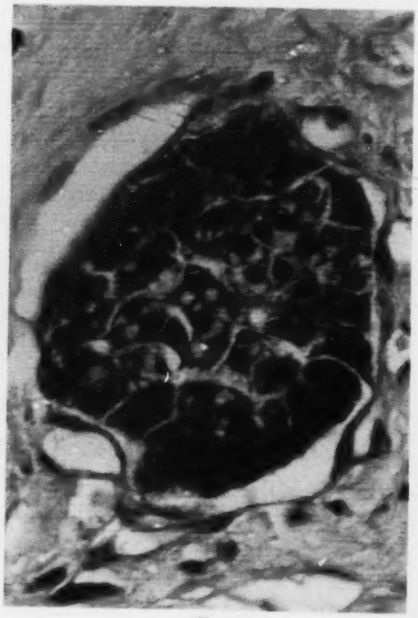

D

C

METASTATIC TUMORS OF THE EXTRAHEPATIC BILIARY TREE

Metastatic tumors to the gallbladder are uncommon, usually asymptomatic, and either discovered at autopsy or incidentally during laparotomy (Botting et al.). The majority result from transcelomic spread and are usually associated with metastatic lesions elsewhere in the abdomen. Grossly, they appear as small single or multiple nodules attached to the serosal surface. The most common primary sites for metastatic carcinomas in the gallbladder are the stomach, pancreas, ovary, bile ducts, colon, and breasts.

Bloodborne metastases to the gallbladder are unusual. They have been reported with malignant melanoma and with carcinomas of the kidney, lung, esophagus, and nasopharynx. These metastatic lesions are single or multiple, commonly invade the mucosa, and may appear several years following removal of the primary tumor. They often begin as submucosal nodules that eventually become pedunculated, and some, especially malignant melanoma and renal cell carcinoma, may even resemble primary malignant tumors of the gallbladder. Primary carcinomas of the liver, however, seldom spread to the gallbladder.

Hematogenous and lymphatic metastases to the bile ducts are unusual. The bile ducts are more often involved by tumor extending directly from adjacent organs.

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MALIGNANT MELANOMA

The most commonly encountered metastatic tumor in both autopsy and surgical material is malignant melanoma. Secondary deposits of melanoma comprise 50 to 66 percent of all gallbladder metastases (Backman). In a study of 125 patients with malignant melanoma, 19 (15 percent) had

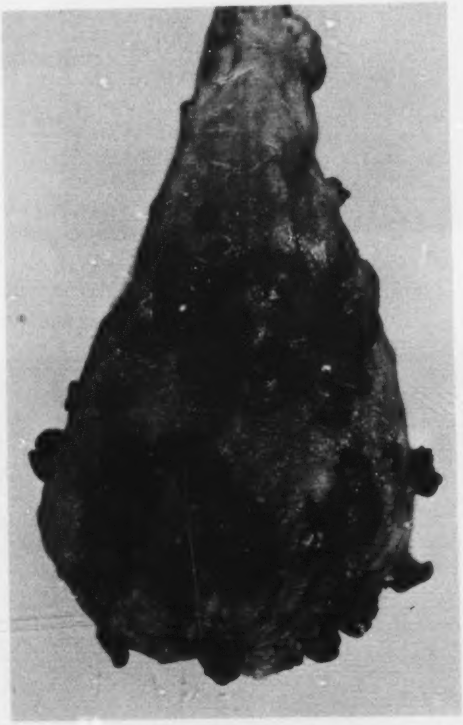

Figure 192
METASTATIC MELANOMA
The gallbladder lumen is exposed. Numerous polypoid melanomatous deposits are shown. (From Shimkin, P.M., Soloway, M.S., and Jaffe, E. Metastatic melanoma of the gallbladder. Am. J. Roentgenol. Rad. Ther. Nucl. Med. 116:393-395, 1972.)

gallbladder metastasis (DasGupta and Brasfield) and in another study of 78 patients, 11 (14 percent) had metastatic involvement of the gallbladder (Shimkin et al.).

Eleven patients with resected metastatic melanoma have also been reported (McFadden et al.). Most of these patients had a history of melanoma that was previously excised from the skin or the eye. They developed biliary symptoms, and cholecystograms usually showed multiple filling defects. The time from diagnosis of the primary tumor to the presentation of gallbladder metastasis has varied from 3 to 13 years, with a mean of 5.8 years.

Grossly, metastatic tumors can involve the serosa or mucosa (Shimkin et al.). Mucosal lesions appear as polypoid masses, either single or multiple, that protrude into the lumen of the gallbladder and which can be a source of confusion with primary malignant melanoma (fig. 192). Microscopically, the tumor is not difficult to recognize since it is often heavily pigmented. Involvement of the gallbladder is usually associated with involvement of the liver.

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MALIGNANT LYMPHOMA AND PLASMA CELL MYELOMA

Malignant lymphoma and plasma cell myeloma may infiltrate the wall of the gallbladder, usually as part of a generalized process. As a rule, it has no clinical significance. Lymphomatous infiltration of the bile ducts can cause obstructive jaundice.

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✣

ASSOCIATION WITH OTHER DISEASES

Cancers of the gallbladder and extrahepatic ducts can occur with other diseases. For instance, carcinoma of the gallbladder occasionally occurs with carcinomas of other sites, including those arising in the stomach, duodenum, or colon (Brandt-Rauf et al.; Burney and Assor). It has been difficult for us to evaluate these cases, but in the absence of any pattern, we consider them examples of coincidental double primary tumors. In our material, 11 percent of patients had a second primary malignant tumor. This high incidence of double primary tumors is attributed to the observation that patients with gallbladder cancer are in older age groups.

We were able to locate three reports of extrahepatic bile duct carcinoma occurring in patients with congenital absence of the gallbladder (Robertson et al.; Richards; Gurll).

There are two reports of biliary tract carcinoma complicating Crohn's disease (Berman et al.; Joffe and Antonioli).

There are three reports of gallbladder carcinoma occurring in patients with multiple polyps of the colon (Kagan and Steckel; Burney and Assor; Bombi et al.). Extrahepatic bile duct cancers have also occurred in patients with familial polyposis coli (Lees and Hermann; Jarvinen et al.).

There is one case report of extrahepatic bile duct carcinoma occurring in a young woman with cystic fibrosis (Abdul-Karim et al.).

More significant is the association of bile duct carcinoma and, to a lesser extent, gallbladder carcinoma with ulcerative colitis. First reported in 1954 as an incidental observation (Parker and Kendall), this association has a common pathologic basis, for there is good radiographic and clinical evidence that the extrahepatic bile ducts are also involved in some patients with chronic ulcerative colitis (Schrumpf et al.; Lupinetti et al.). This involvement usually takes the form of chronic sclerosing cholangitis, which is characterized by progressive inflammation and fibrosis of the extrahepatic ducts.

Patients with ulcerative colitis can develop either carcinoma of the extrahepatic bile ducts or sclerosing cholangitis, or both. It is our opinion that sclerosing cholangitis occurs in many patients with ulcerative colitis and is possibly a forerunner of carcinoma. In some cases, evidence of sclerosing cholangitis was present before carcinoma developed, and some patients even had transient episodes of jaundice. Carcinoma may develop years after proctocolectomy, which seems to suggest that the disease process may continue in the biliary passages even after removal of the involved colon.

Patients who develop biliary tract carcinoma as a complication of ulcerative colitis are younger than those with spontaneous biliary tract cancer, and usually do not have gallstones (Morowitz et al.; Ross and Braasch). Furthermore, they often have a long history of colitis – mean duration 15 years with medical treatment – and extensive involvement of the colon. It has been estimated that these tumors are 10 times more frequent in patients with ulcerative colitis than in the general population (Ritchie et al.). As for the pathogenesis, it seems reasonable to conclude that the same inflammatory process involves the bile ducts as well as the colon and that biliary epithelium, because of the inflammatory changes and immune response, becomes more susceptible to malignant transformation, just as colonic mucosa is more susceptible in this disease.

In patients with extrahepatic bile duct cancer associated with ulcerative colitis, there is no difference in the histologic appearance, sites of origin, or subsequent clinical course compared to patients with spontaneous biliary tract cancer.

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UNCLASSIFIED AND RARE LESIONS

Tumors that do not fit into current classification schemes can arise in the extrahepatic biliary tree. The example shown in figures 193 and 194 occurred in the gallbladder and was considered to be a type of endocrine tumor by some pathologists, primitive hepatic tumor by others, and a leiomyoblastoma by still others.

Another case, shown in figure 195, was initially considered an adenocarcinoma of the cystic duct. However, because of the endocrine arrangement of the cells and age of the patient (28 years), immunohistochemical studies were performed which revealed somatostatin (pl. IV-D; Goodman et al.). This tumor, composed of clear cells

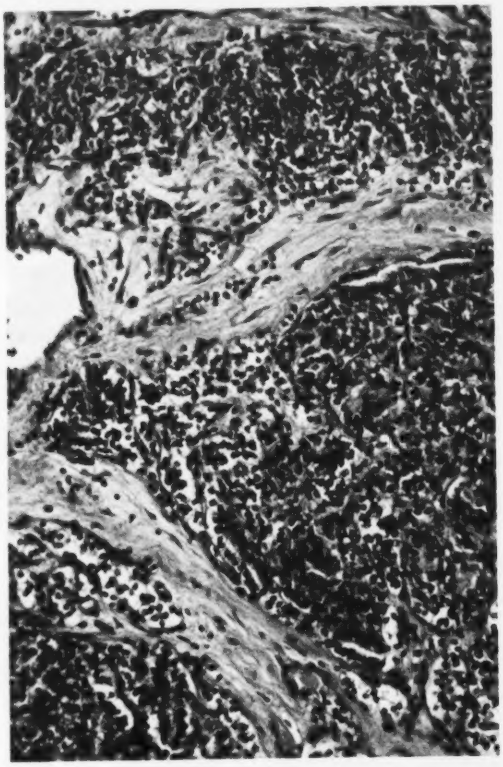

Figure 193
(Figures 193 and 194 from same patient)
UNCLASSIFIED TUMOR
The tumor is composed of lobules separated by fibrous connective tissue. Most cells have clear cytoplasm that is rich in glycogen. Small tubular structures are seen at the periphery of one lobule. This tumor was variously interpreted as an endocrine tumor, leiomyoblastoma, or a primitive hepatic tumor. X160.

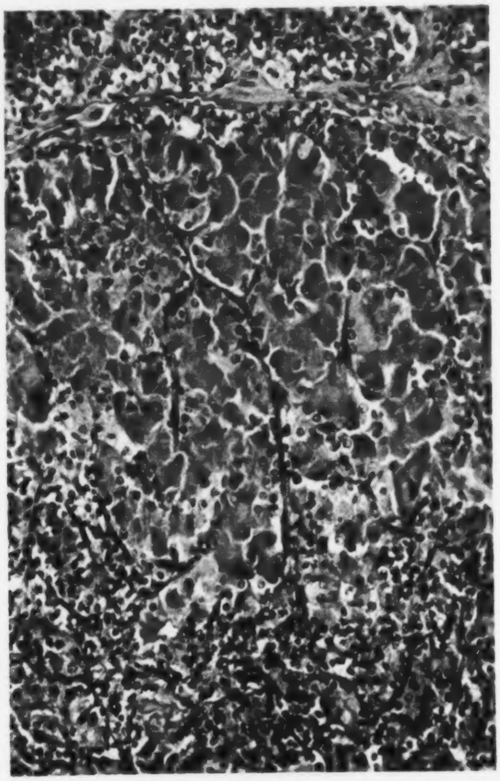

Figure 194
UNCLASSIFIED TUMOR
Higher magnification of another lobule from figure 193, showing two cell types. One is small, with a clear cytoplasm that contains glycogen, and the other type is large, with an eosinophilic cytoplasm. These large eosinophilic cells resemble oncocytes. Between the cells, many capillaries are seen. X250.

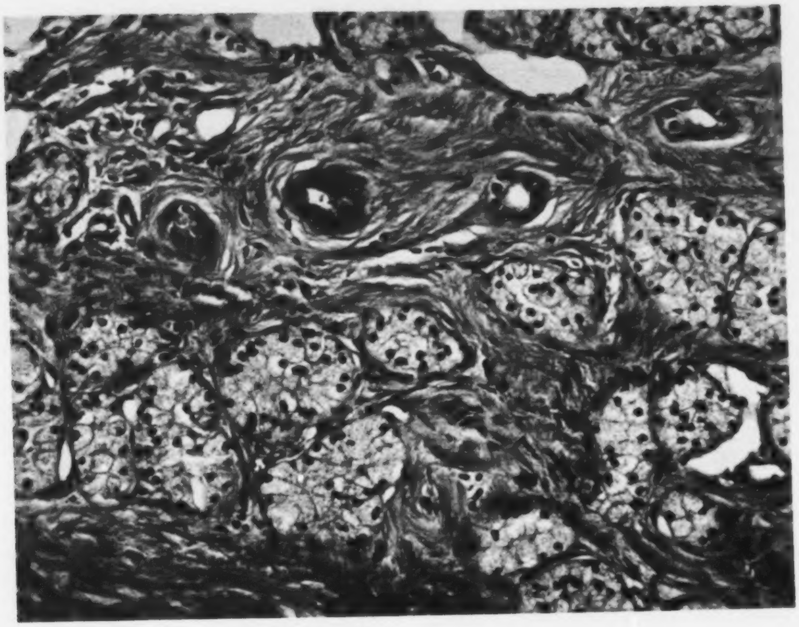

Figure 195
(Figure 195 and plate IV-D from same patient)
D CELL CARCINOMA OF CYSTIC DUCT
Cords and nests composed of clear cells, with small hyperchromatic basal nuclei and abundant clear cytoplasm, have infiltrated the fibrotic wall of the cystic duct. Some small normal bile ducts are also present. Tumor had metastasized to a regional node. X250. (Courtesy of Dr. Z. Goodman, Washington, D.C.)

arranged in cords, trabeculae, and small nests, is similar to the somatostatinomas reported in the duodenum (Kaneko et al.) and in the jejunum (Alumets et al.). Contrary to what has been observed with D cell tumors in the pancreas, this somatostatinoma in the cystic duct did not cause the endocrine syndrome attributed to excessive secretion of somatostatin.

It is possible that with the use of immunohistologic technics, other endocrine tumors will be found in the biliary tract.

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PRIMARY SCLEROSING CHOLANGITIS

SYNONYMS AND RELATED TERMS: Fibrosing cholangitis; obliterative cholecystitis; stenosing cholangitis.

Recognized since 1924, primary sclerosing cholangitis has become an important consideration in the differential diagnosis of extrahepatic bile duct cancer. The disease, which may involve any or all parts of the biliary tree, is characterized by progressive inflammation and fibrous thickening of the bile ducts (fig. 196). It has an uncertain but generally poor prognosis, no known etiology, and is usually treated empirically. Clinically, it is first manifested by transient episodes of cholestasis. The disease is uncommon, occurring less often than secondary types of sclerosing cholangitis, from which it should be differentiated (Longmire). Death usually results from liver failure or septicemia.

Clinically and morphologically, the disease resembles cancer. The clinical manifestations – progressive jaundice in the absence of stones, infection, or previous surgery – can suggest a diagnosis of extrahepatic bile duct cancer (Beachley and Landau). Histologically, the disease is characterized by a normal or ulcerated mucosa, lymphocyte aggregates in the lamina propria, glandular distortion, fibrosis, and stenosis of the extrahepatic and, in some cases, the intrahepatic bile ducts as well (figs. 197, 198). As a result of fibrosis, the bile ducts may be focally or diffusely thickened and are often described as ropelike. In many cases, biopsy of the liver reveals chronic inflammation in portal areas (pericholangitis) or changes that are difficult to distinguish from primary biliary cirrhosis.

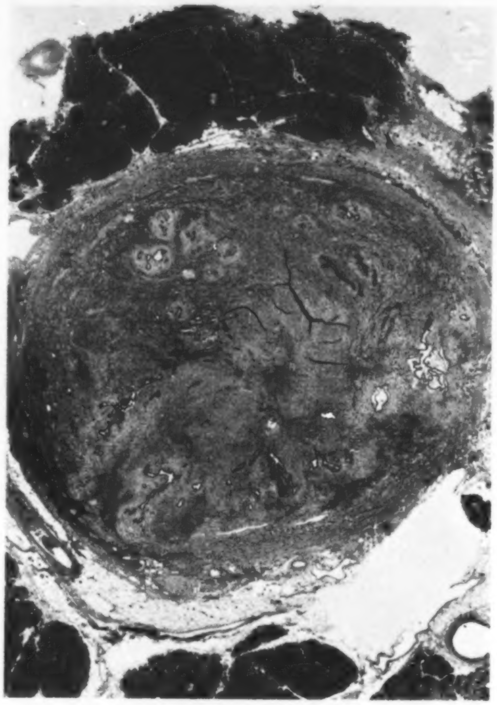

Figure 196
(Figures 196–198 from same patient)
PRIMARY SCLEROSING CHOLANGITIS
Cross section through the common duct, showing obliteration of the lumen and fibrous thickening of the wall. X4.

While biopsies of the bile ducts and liver are helpful in the diagnosis, the histologic changes are nonspecific and a diagnosis of primary sclerosing cholangitis is usually made by exclusion. Types of secondary cholangitis that should be excluded are caused by infection, stones, congenital anomalies, trauma such as penetrating wounds, and previous surgery (the most common cause).

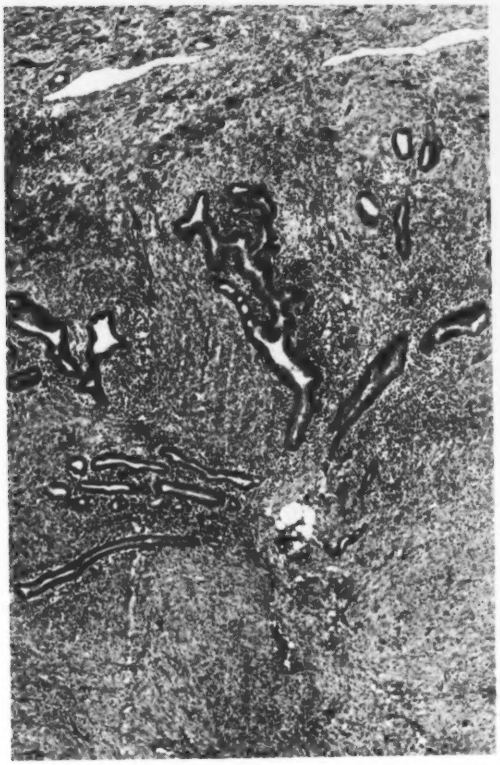

Figure 197
PRIMARY SCLEROSING CHOLANGITIS
Higher power of figure 196, showing distortion and proliferation of intramural glands which lie in dense fibrous tissue that contains some inflammatory cells. X43.

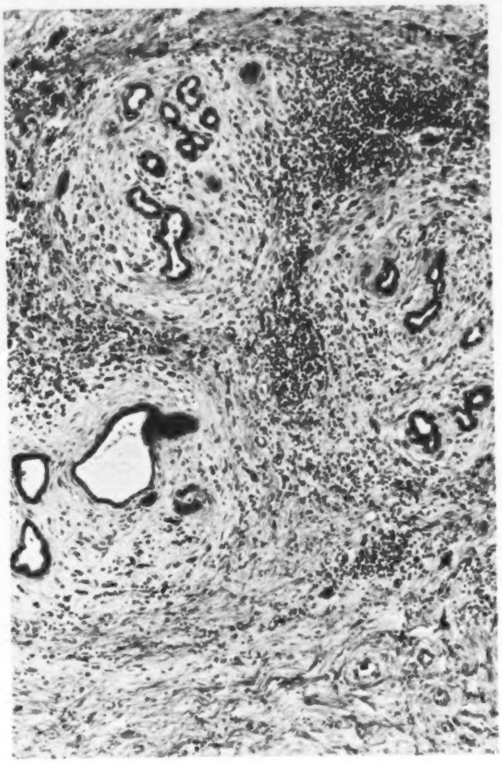

Figure 198
PRIMARY SCLEROSING CHOLANGITIS
Higher magnification of figure 196. The distorted glands, which appear to be arranged in lobules, are surrounded by concentric rings of fibrous tissue. Chronic inflammatory cells are also present. X80.

As a result of fibrosis and inflammation, the glands are distorted and displaced, changes which can simulate a well differentiated adenocarcinoma (figs. 197, 198). Alternatively, in cases of well differentiated adenocarcinomas, the neoplastic glands can grow along the wall of the bile ducts for some distance without causing a nodular mass. These glands, along with attendant desmoplasia and inflammation, can resemble the changes in sclerosing cholangitis (fig. 199).

The differential diagnosis between sclerosing cholangitis and infiltrating carcinoma can be difficult, especially with a small biopsy, and may not be possible in some cases. The difficulties have been emphasized (Altemeier et al.; Longmire; Peck et al.). In addition to the usual criteria for malignancy, the following should be useful: The presence of normal mucosa in the biopsy does not exclude carcinoma, since a tumor may extend along the wall for some distance beneath the mucosa. Nuclear

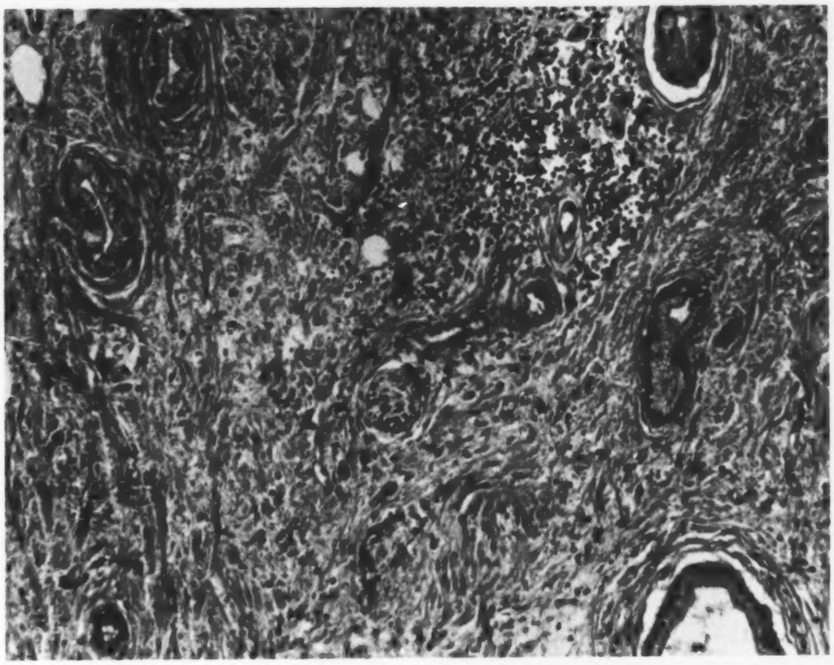

Figure 199
LEFT HEPATIC DUCT ADENOCARCINOMA
A well differentiated adenocarcinoma of the left hepatic duct shows scattered glands separated by dense fibrous stroma in which are some inflammatory cells. This histologic pattern can be mistaken for primary sclerosing cholangitis. X125.

hyperchromatism and epithelial atypia are found in both conditions and may not be reliable. Cancerous glands, on the other hand, often infiltrate small nerves located around the bile ducts, whereas the glands in sclerosing cholangitis do not invade nerves. This nerve invasion, which is one of the more important features, may even be seen on frozen section. In carcinomas, the neoplastic glands infiltrate the wall in a random and diffuse manner and often extend into periductal tissues. Occasionally, in cases of sclerosing cholangitis, the radial and orderly arrangement of glands around the lumen is still evident. Also, in cases of primary sclerosing cholangitis, the fibrosis may have a concentric arrangement around the glands, a feature that we have not seen in carcinomas (fig. 198). Finally, in carcinoma, the number of neoplastic glands may exceed the number of normal glands expected in the section. In general, the pattern of invasion may be more helpful than the appearance of individual glands. Some cases may even require regional metastasis before a diagnosis can be safely made. Bile should be collected for cytology in all cases.

The cholangiographic appearance is often characteristic due to the segmental or diffuse narrowing of the extrahepatic ducts. However, if the procedure fails to demonstrate the biliary tract because of elevated levels of serum bilirubin, retrograde cholangiography can be used to make the diagnosis. In some patients, the bile ducts may return to normal radiographically (Thompson et al.).

Sclerosing cholangitis is often associated with other diseases, most commonly with ulcerative colitis. It has also been reported in association with a variety of chronic fibrosing conditions such as retroperitoneal fibrosis, mediastinal fibrosis, Peyronie's disease, Riedel's struma, Crohn's disease, sclerosis of the salivary glands and pancreas, and pseudotumor of the orbit (Caroli and Rosner). Primary sclerosing cholangitis has occurred in a renal transplant recipient (Thompson et al.) and in children (Werlin et al.; Spivak et al.). It has also been associated with angioimmunoblastic lymphadenopathy (Bass et al.). Because of its association with other diseases, primary sclerosing cholangitis is probably one manifestation of a much larger disease complex that includes inflammatory bowel disease, primary biliary cirrhosis, and other progressive fibrosing lesions.

The etiology is still controversial. Its occurrence with certain diseases thought to have an immunologic basis suggests that primary sclerosing cholangitis is the result of an autoimmune process. Some believe, on the basis of experimental studies, that cellular immune responses to specific biliary antigens are involved in the progressive bile duct destruction (McFarlane et al.). The serum mitochondrial antibody test, which is positive in a large percentage of patients with primary biliary cirrhosis, is usually negative in cases of sclerosing cholangitis (Chapman et al.).

The increased incidence of bile duct carcinoma in patients with ulcerative colitis and the role of primary sclerosing cholangitis are discussed on page 190. Bile duct carcinoma can develop after long-standing primary sclerosing cholangitis (Chapman et al.).

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AFTERTHOUGHT

Since publication of the original Fascicle on Gallbladder and Extrahepatic Biliary Tumors, our knowledge of these lesions has substantially increased. Even though we have tried to incorporate this new knowledge into this second Fascicle, perhaps the best way to summarize this increase is to compare the pathologic changes in the gallbladder with those in the intestine.

The gallbladder is a specialized endodermal derivative, but its response to injury and the characteristics of its neoplasms share many features with those of the intestine. For example, carcinomas of the gallbladder are known to produce Krukenberg tumors of the ovary which are also caused by gastric and other intestinal neoplasms. The gallbladder epithelium elaborates more CEA as it evolves into in situ and invasive carcinomas, and the gallbladder can give rise to intestinal-type adenocarcinomas. Often, in cases of cholecystitis, the epithelium undergoes intestinal metaplasia which, we believe, is analogous to the process of intestinal metaplasia that occurs in the stomach. In both the stomach and gallbladder, the number of endocrine cells increases in these areas of metaplasia. Diffuse infiltration of the gallbladder wall by some neoplasms calls to mind the diffuse infiltration of the stomach wall by some gastric cancers, especially signet ring cell carcinomas. Future research will continue, most likely, to reveal other similarities between pathologic changes in the gallbladder and those in the intestine. It is through such comparisons, we believe, that our understanding of gallbladder pathology can be placed in broader perspective.

Unifying Concept

Many carcinomas arising in the gallbladder are histologically similar to those originating from other endodermal derivatives, especially from the foregut. For instance, pleomorphic giant cell carcinomas occur in the gallbladder, thyroid, lung, and pancreas, organs which are all forgut derivatives. Similarly, osteoclastoma-like areas occur in carcinomas of the gallbladder, pancreas, liver, lung, and thyroid. Although the incidence of these tumors may be different for each site, their histologic similarity suggests a common pathway of development based on a common embryologic origin, and may also suggest common treatment regimens.

As a unifying concept, therefore, the types of pathologic changes and responses to injury encountered in the biliary system are best explained embryologically. As a derivative of the foregut, the gallbladder displays many histologic changes common to other foregut derivatives. In fact, these common changes raise the question of whether we should consider these derivatives (liver, biliary tree, pancreas, stomach, esophagus, lung, thyroid, and thymus) as a single anatomic unit. For instance, enterogenous cysts are found in the anterior mediastinum, and small clusters of mucin-secreting goblet cells occur in some thymomas. Chronic thyroiditis is sometimes associated with atrophic gastritis, and as the incidence of goiter has declined in the United States, so has stomach cancer. In addition, carcinomas of the gallbladder can elaborate products associated with other yolk sac derivatives, such as alpha-fetoprotein. In summary, the gallbladder does not appear different from other organs, since the pathologic lesions that occur in the gallbladder also occur in other parts of the intestine.

Anatomic Considerations

On first encounter, cancers of the gallbladder seem more malignant than cancers in other organs because they rapidly cause death. This difference, however, is only an illusion, the result of the strategic location of the gallbladder and late diagnosis. There is no evidence that carcinomas of the gallbladder grow faster or that they are more invasive than corresponding tumors in other sites. Most carcinomas do not contain large numbers of mitotic figures nor appear to have high growth rates. Invasion and local extension which probably involve the same mechanisms used by other tumors are facilitated by anatomic factors. These include the thin wall, growth into Rokitansky-Aschoff sinuses, and the continuity of the perimuscular connective tissue of the gallbladder with the interlobular connective tissue of the liver.

Heterogeneity

In carcinomas of the gallbladder, the pathologist is confronted with a spectrum of morphologic patterns, a comment frequently made by observers of this disease. We believe there are two reasons for this spectrum. The first is that the gallbladder gives rise to tumors that are related to its normal structure; these include well differentiated adenocarcinomas and oat cell carcinomas. The second reason depends upon its embryologic origin. The gallbladder can also give rise to tumors with structural features related to its tissue of origin; these include intestinal-type and signet ring cell carcinomas, the latter usually associated with the stomach.

Most carcinomas of the gallbladder are histologically labile; that is, they can form multiple patterns within the same tumor. For instance, in well differentiated adenocarcinomas, which comprised 48 percent of all carcinomas in our series, these patterns can include focal areas of intestinal-like glands, squamous cells, clear cells, or even signet ring cells. In contrast, 15 to 30 percent of the other types show focal areas of a well differentiated adenocarcinoma.

Differentiation of gallbladder carcinomas occurs at both the histologic and cellular level. Histologic differentiation includes formation of squamous cells, glandular structures, or ribbons and festoons and is the basis for the current classification. But preeminent over histologic differentiation is cellular differentiation, which includes formation of tonofilaments, mucin droplets, microvilli, secretory granules, and desmosomes, structures associated with specific differentiated cell types. It appears, based on our ultrastructural studies of gallbladder carcinomas, especially adenosquamous carcinomas, that patterns of intracellular differentiation are not mutually exclusive, but that individual tumor cells can form various structures, such as mucin droplets and tonofilaments, which are normally associated with different cell types.

Because intracellular differentiation is not mutually exclusive, we can expect various combinations such as the presence of CEA in squamous cell tumors, or adenocarcinomas that contain mucin and tonofilaments. Perhaps the synthesis of tonofilaments in a glandular tumor is analogous to the synthesis of ectopic hormonal peptides by some carcinomas.

Clinical Concerns

In dealing with carcinoma or other diseases of the biliary tract, the physician is invariably faced with the perpetual problem of biliary obstruction and its differential diagnosis. Although the causes of bile duct obstruction are legion and cannot all be considered here, they vary in frequency with age, geography, and sex. In children, for example, they include rhabdomyosarcoma, retroperitoneal fibrosis, inflammatory polyp of the common bile duct, congenital anomalies, choledochal cysts, parasites, pancreatitis, Caroli's disease, and benign tumors such as granular cell tumors.

We did not discuss the controversy concerning cholecystectomy for cholelithiasis as a prevention for gallbladder carcinoma, but it seems reasonable that cholecystectomy should be performed if the stones cause symptoms. In areas where the incidence of gallbladder cancer is high, surgeons should probably be more aggressive in performing prophylactic cholecystectomies and in using newer diagnostic technics such as gallbladder puncture during peritoneoscopy accompanied by bile cytology.

Histogenesis

Squamous cell carcinomas in all probability arise from metaplastic squamous epithelium, and intestinal type adenocarcinomas from areas of intestinal metaplasia. With these two exceptions, we assume that all other carcinomas arise from some endodermal stem cell within the columnar epithelium, but the factors that cause this stem cell to differentiate into various phenotypes, such as colloid carcinomas or pleomorphic giant cell carcinomas, are unknown. On the assumption that such a stem cell has an equal probability of differentiating into any tumor phenotype, these factors must then depend on either the etiology or the interaction with other cells. The latter is probably more important, since it can also explain the multiple patterns observed in most gallbladder carcinomas.

Epidemiology

Since the gallbladder is not open to the environment like the intestine, it seems reasonable to assume that the etiology of gallbladder and, perhaps, bile duct carcinoma is dependent upon the secretory products in bile. Differences in the composition of bile of certain racial groups are now known. For example, American Indians have greater amounts of cholesterol than Caucasians, and Bolivians have greater amounts of glycolithocholic acid than Caucasians, although these differences have not as yet been correlated with the development of cancer. Furthermore, careful analytic biochemistry might reveal other components in bile that are presently unknown and occur in very low concentrations.

The importance of epidemiologic studies in understanding the etiology of gallbladder cancer cannot be underestimated. The different racial and geographic distributions, as discussed in this Fascicle, compel further study, especially into dietary habits, genetics, and bile composition. We anticipate that the results of epidemiologic studies will stimulate important research in this area. Furthermore, the results of epidemiologic studies will be carefully considered by those interested in colon cancer, since bile salts may also be a factor in cancer of the large intestine.

Biologic Properities

Oat cell carcinomas of the gallbladder, like those of the lung, may produce ectopic peptide hormones, presumably by derepression of the genome that controls these hormones. However, we want to extend this concept of derepression to the other functions of malignant cells, functions that also occur in normal differentiated cells. It seems reasonable that by derepression of genomes that control these other functions, a cell acquires certain properties that we have come to associate with malignancy. For example, the motility of malignant cells may involve the same mechanism as that of a leukocyte; proteases necessary for tumor invasion may be the same enzymes involved in migration of embryonic cells and remolding of normal tissues; the mechanism of phagocytosis by tumor cells may be the same as that of macrophages; and differentiated of malignant cells into squamous or other types may involve the same process as normal differentiation.

Final Remarks

Finally, in many textbooks of pathology, cancer is defined as a progressively growing mass of abnormal tissue. This definition, which applies to cancer of the gallbladder and extrahepatic bile ducts, does not take into account the observation that malignant tumors are heterogeneous. As exemplified by gallbladder cancer, they are heterogeneous histologically, both in cell type and growth patterns, and according to recent research on other tumors, are probably heterogeneous with respect to biochemistry and function. For instance, only 25 percent of biliary tract tumors produce alpha-fetoprotein. Newer definitions should consider this heterogeneity which pathologists often confront in their differential diagnoses. We believe that this heterogeneity is an important consideration in the biology of cancer and that the multiple histologic patterns represent one of the fundamental properties of neoplasia.

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